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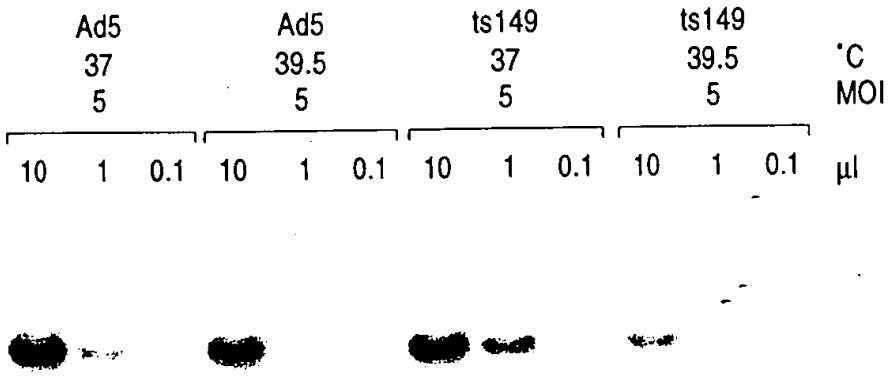

Ad5
37
5
Ad5
39.5
5
ts149
37
5
ts149
39.5
5
°C
MOI
10 1 0.1 10 1 0.1 10 1 0.1 10 1 0.1 µl

Figure 1

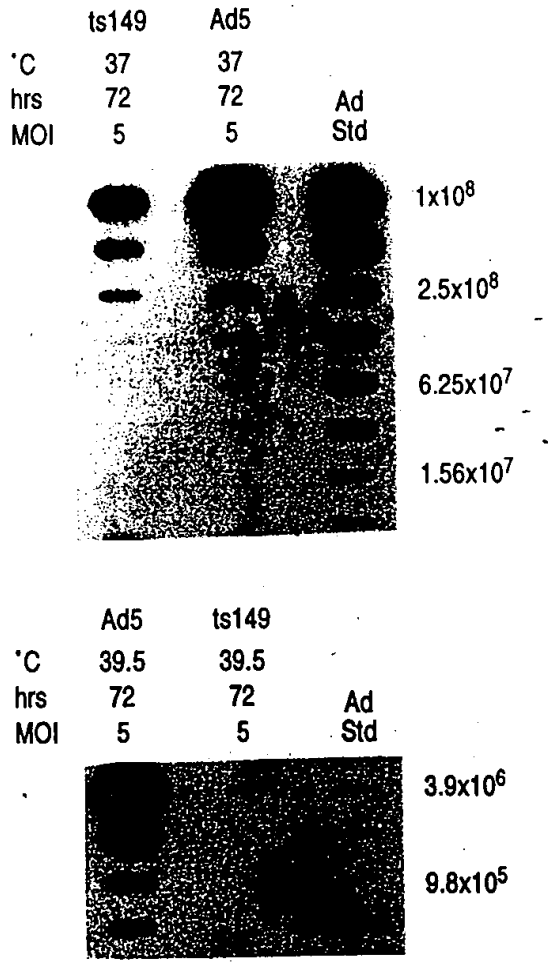

ts149
Ad5
°C
37
37
hrs
72
72
MOI
5
5
Ad Std
1x10^8
2.5x10^8
6.25x10^7
1.56x10^7
Ad5
ts149
°C
39.5
39.5
hrs
72
72
MOI
5
5
Ad Std
3.9x10^6
9.8x10^5

Figure 2

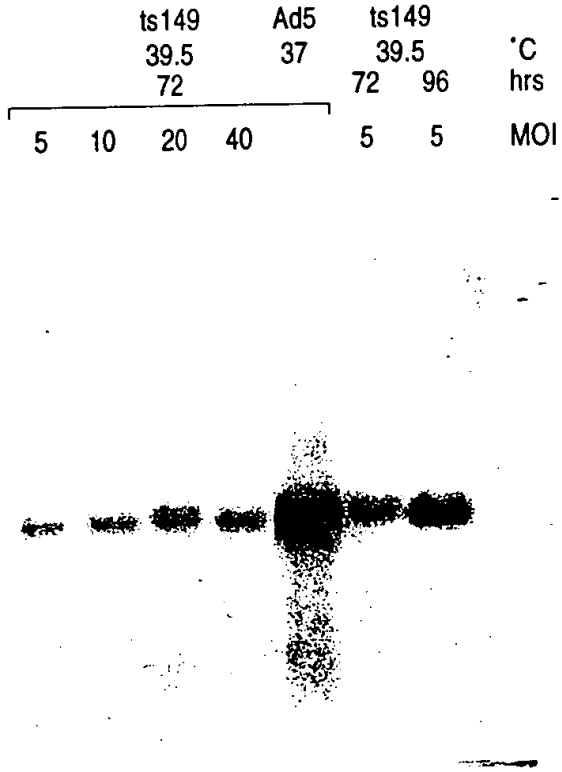


Figure 3

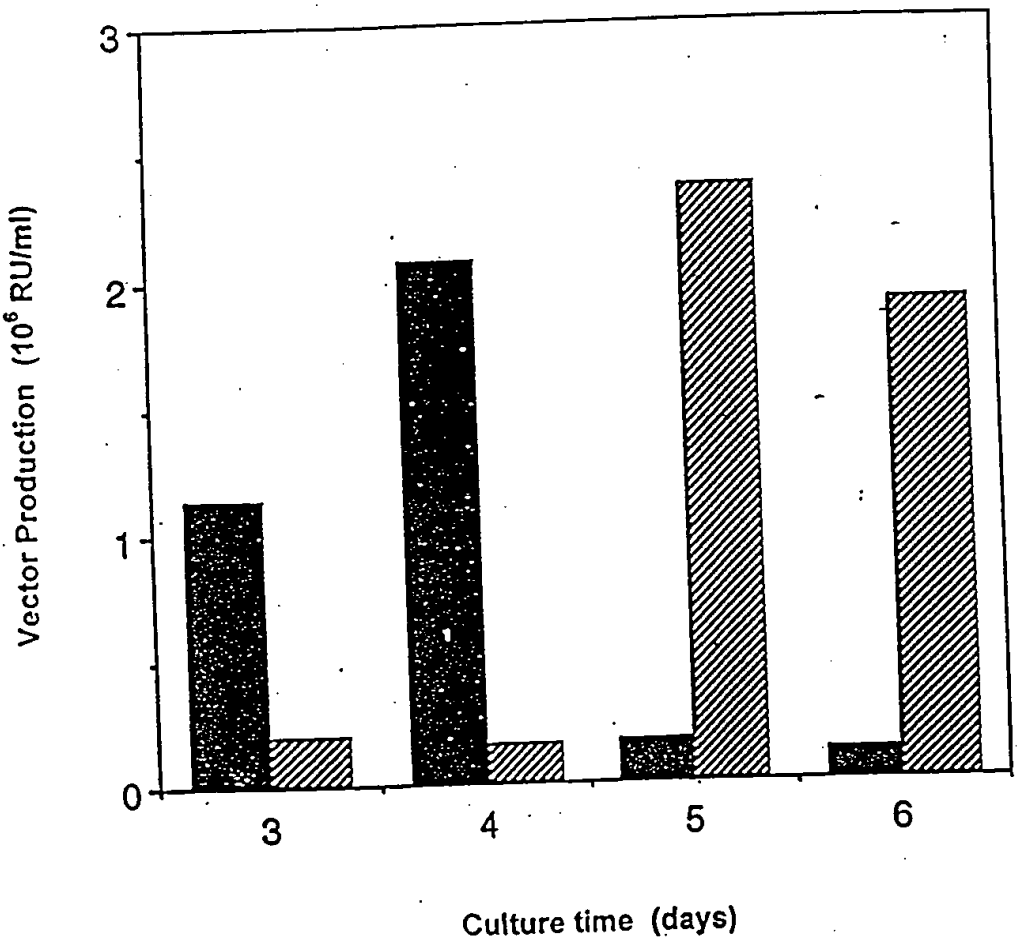


Figure 4

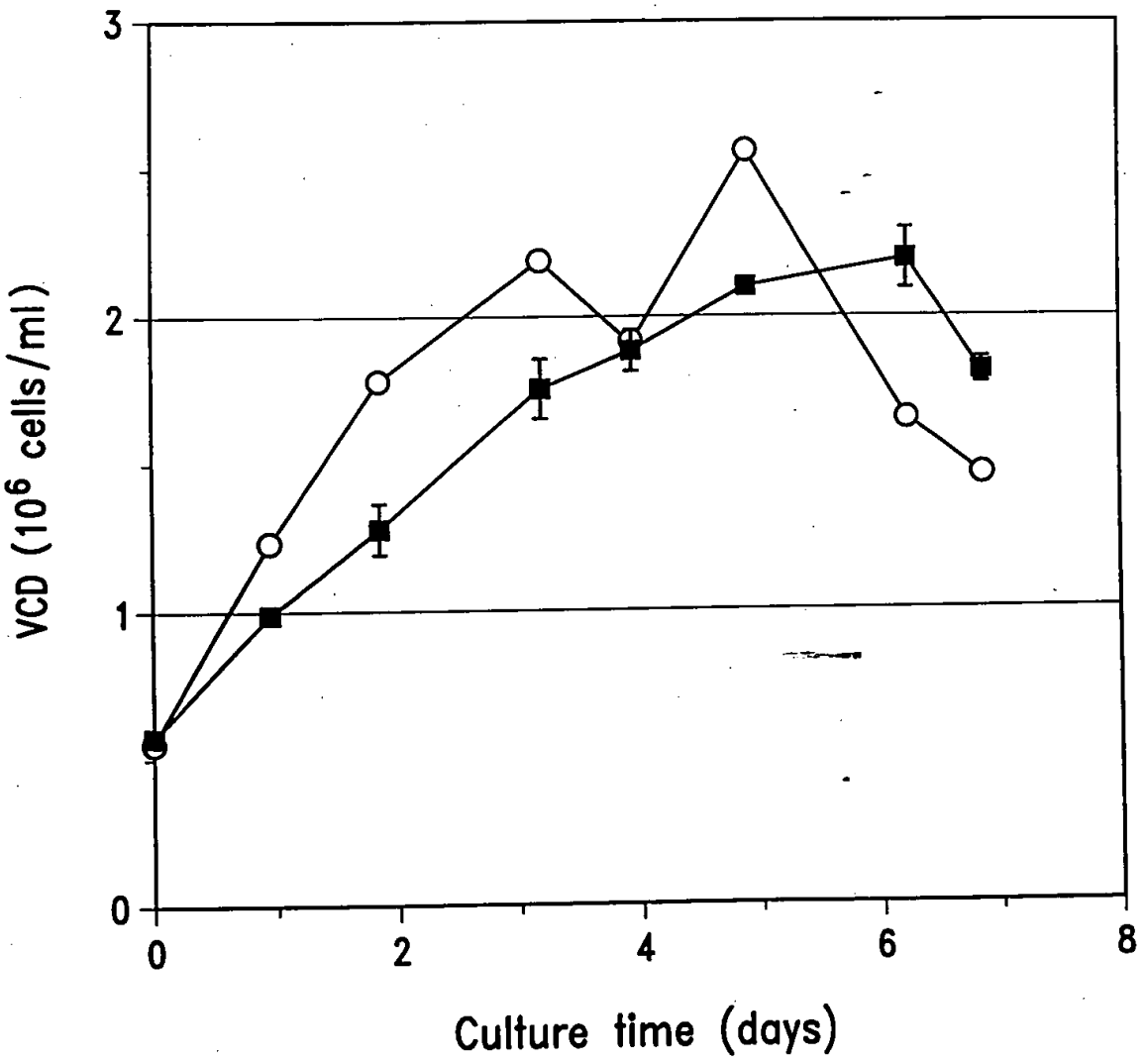


Figure 5

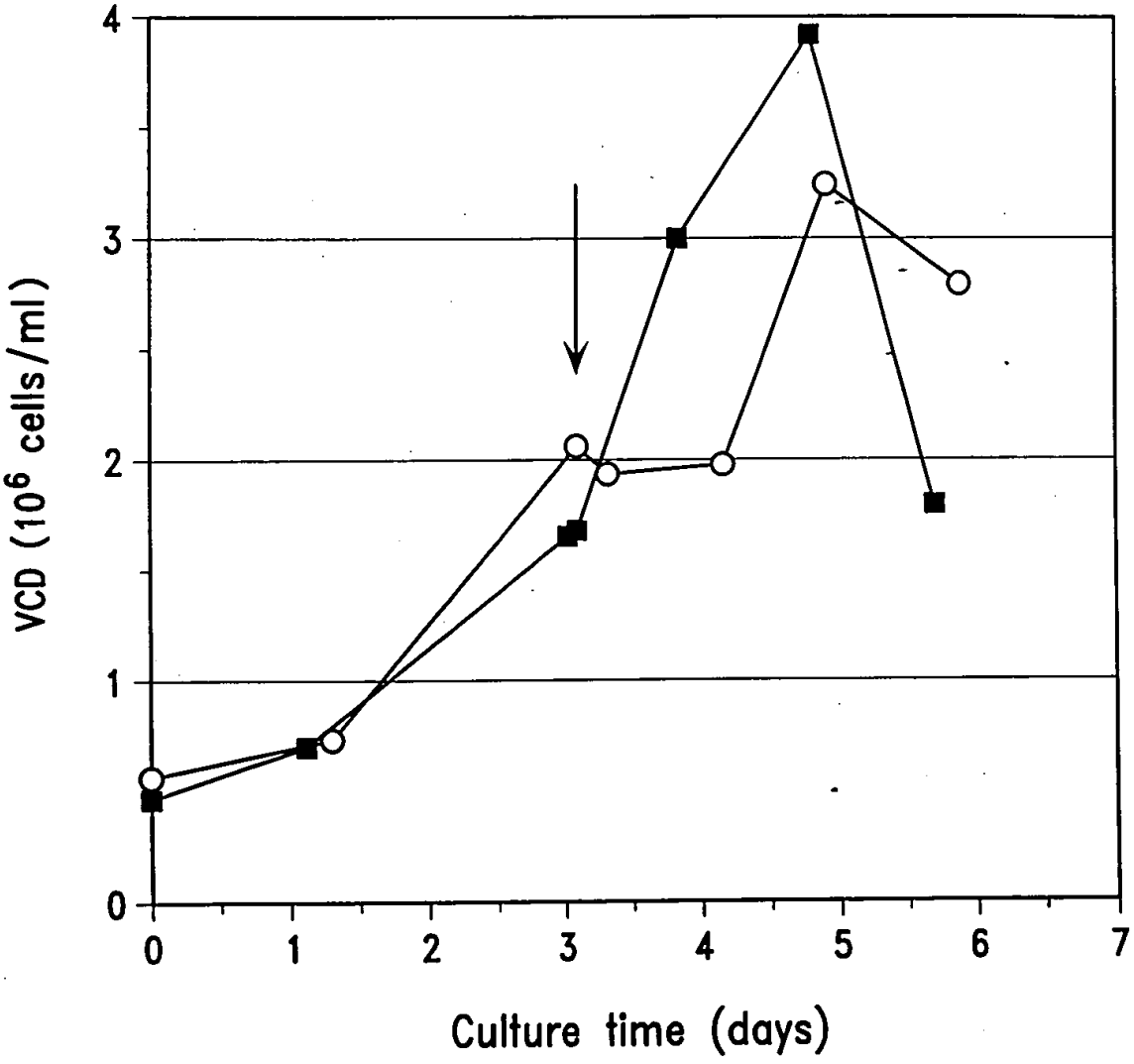


Figure 6

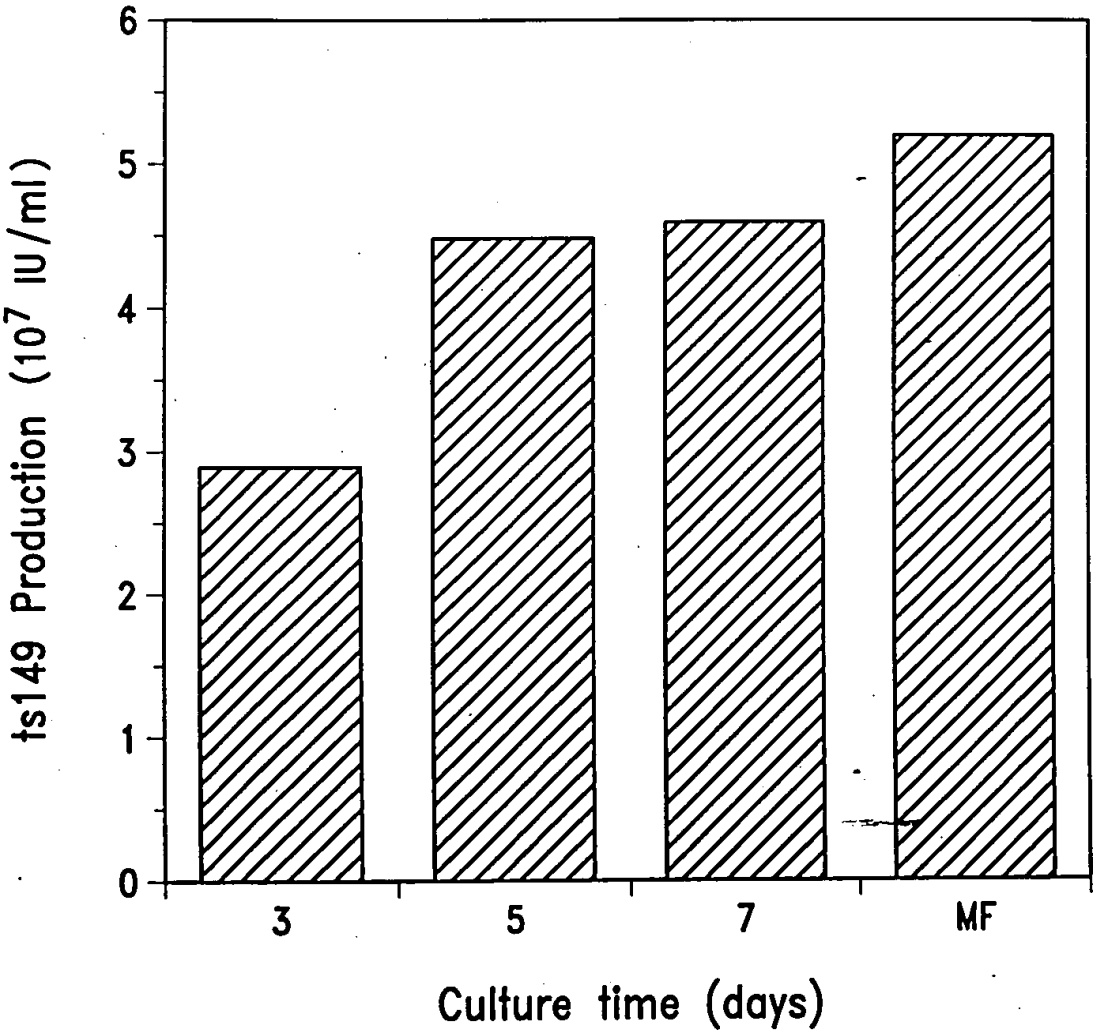


Figure 7

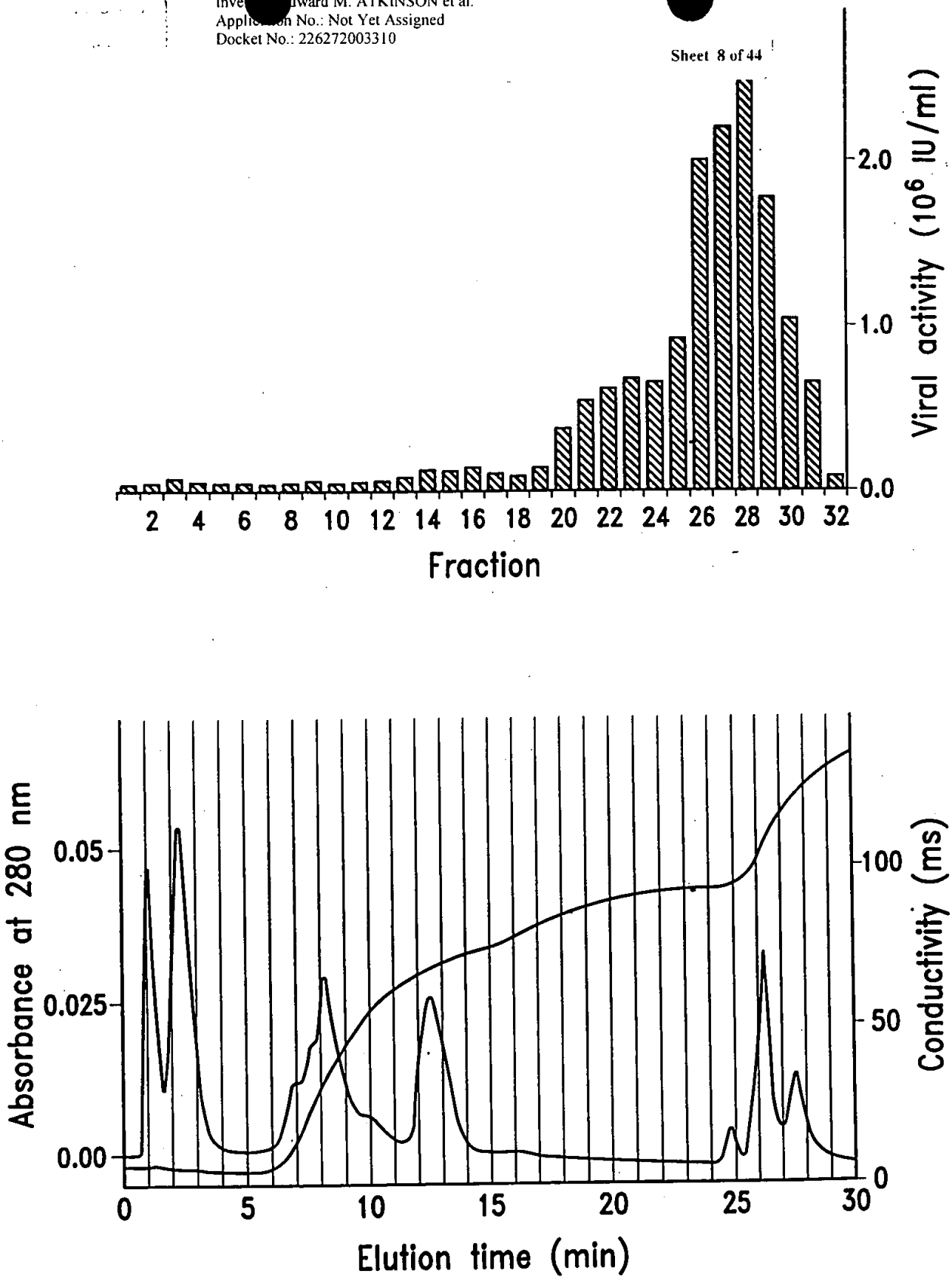

Viral activity (10^6 IU/ml)
2.0
1.0
0.0
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Fraction
Absorbance at 280 nm
0.05
0.025
0.00
Conductivity (ms)
100
50
0
0 5 10 15 20 25 30
Elution time (min)

Figure 8

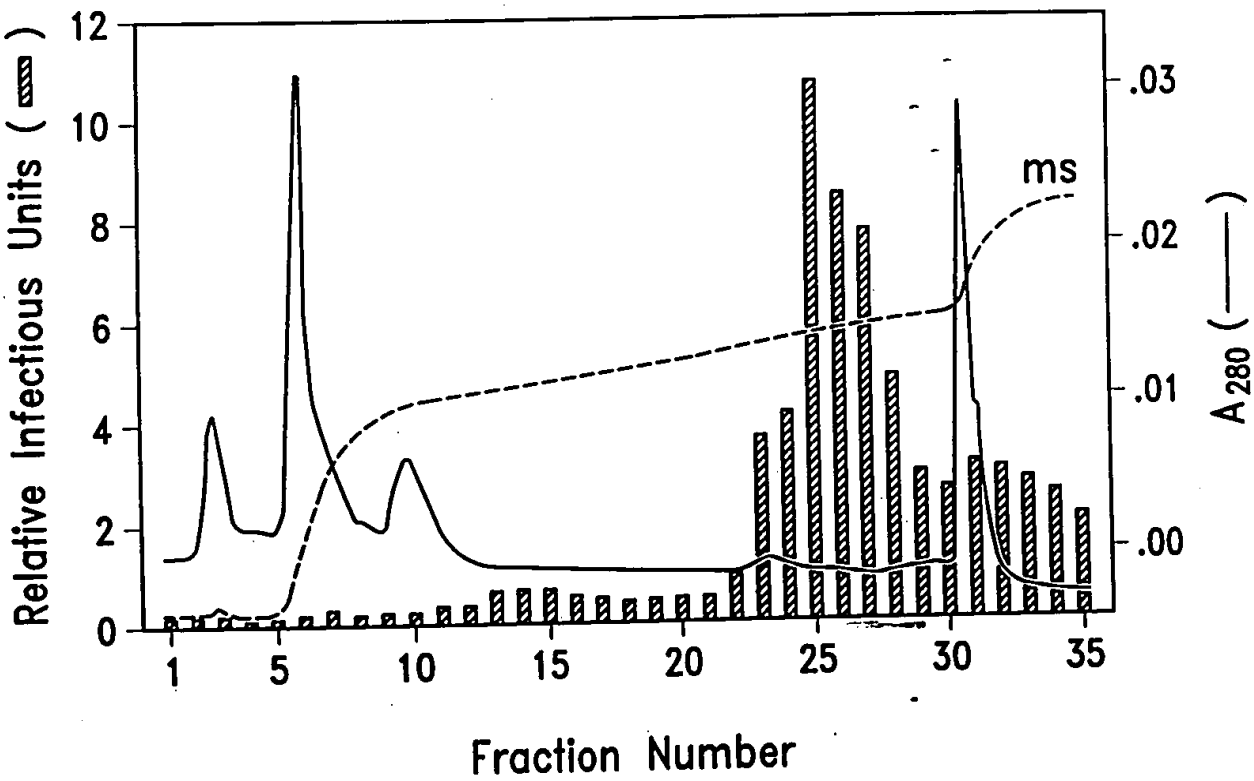

Relative Infectious Units ( )
12
10
8
6
4
2
0
1
5
10
15
20
25
30
35
Fraction Number
ms
.03
.02
.01
.00
A280 ( )

Figure 9

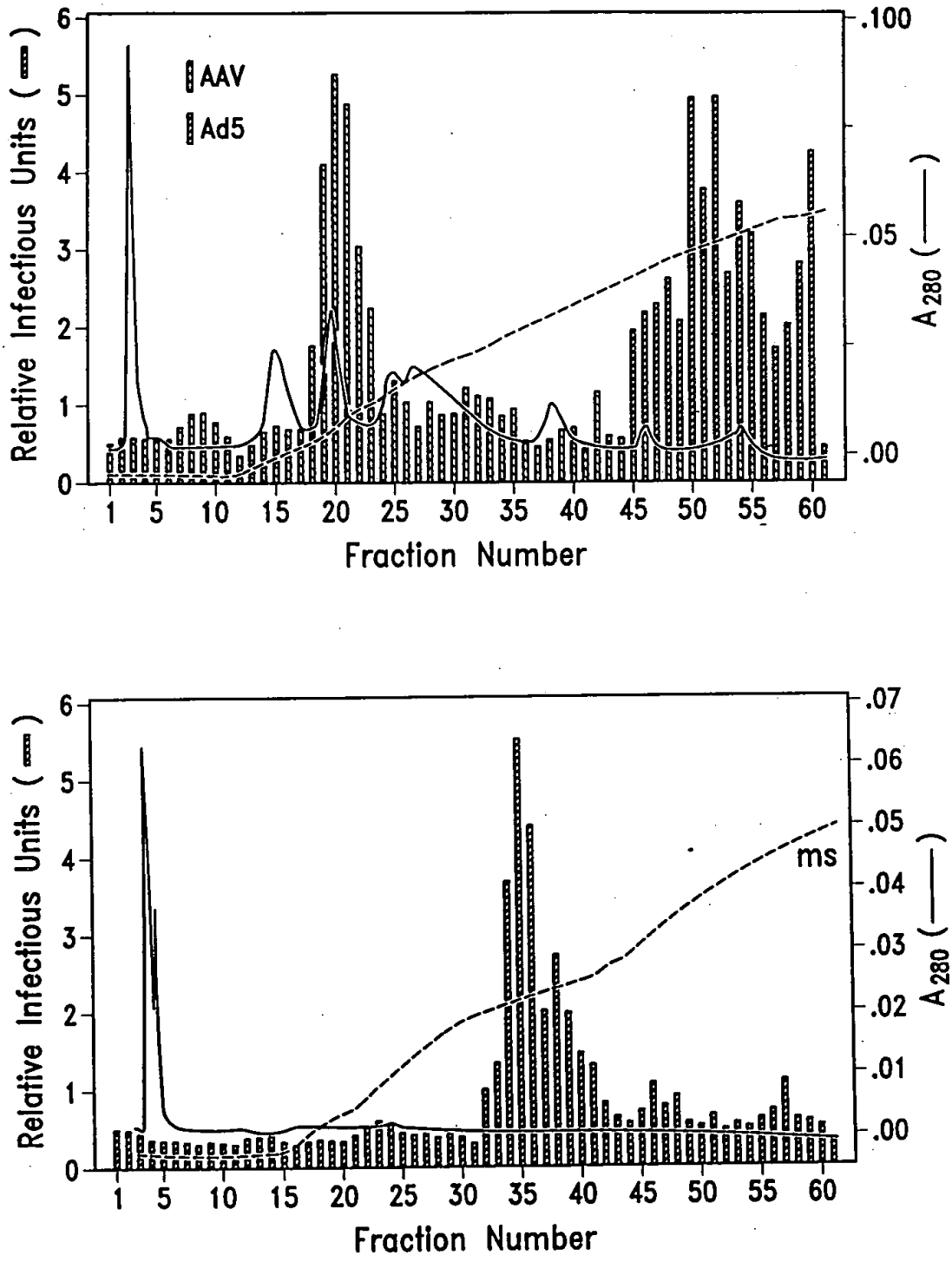
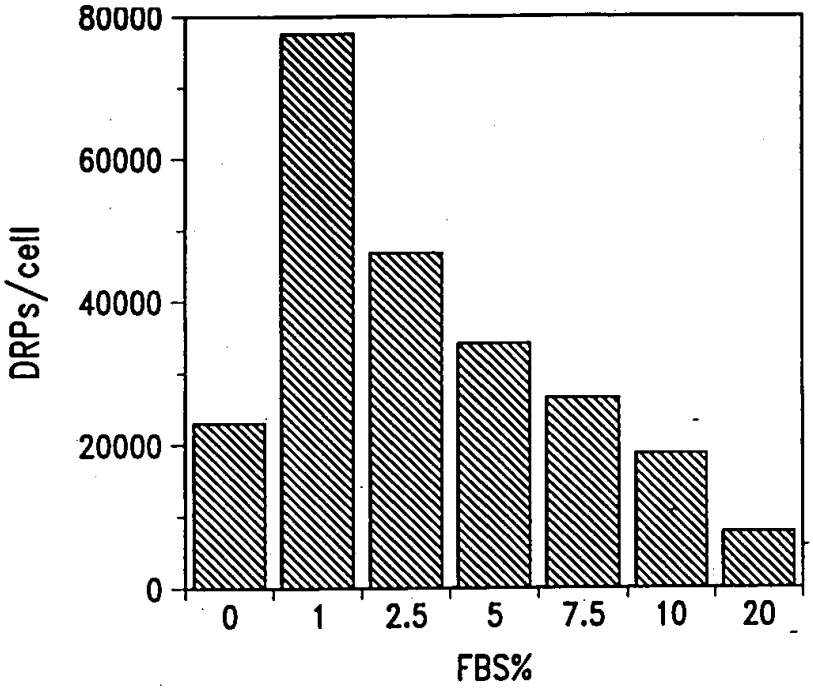


Figure 10


80000
60000
40000
20000
0
DRPs/cell
0
1
2.5
5
7.5
10
20
FBS%

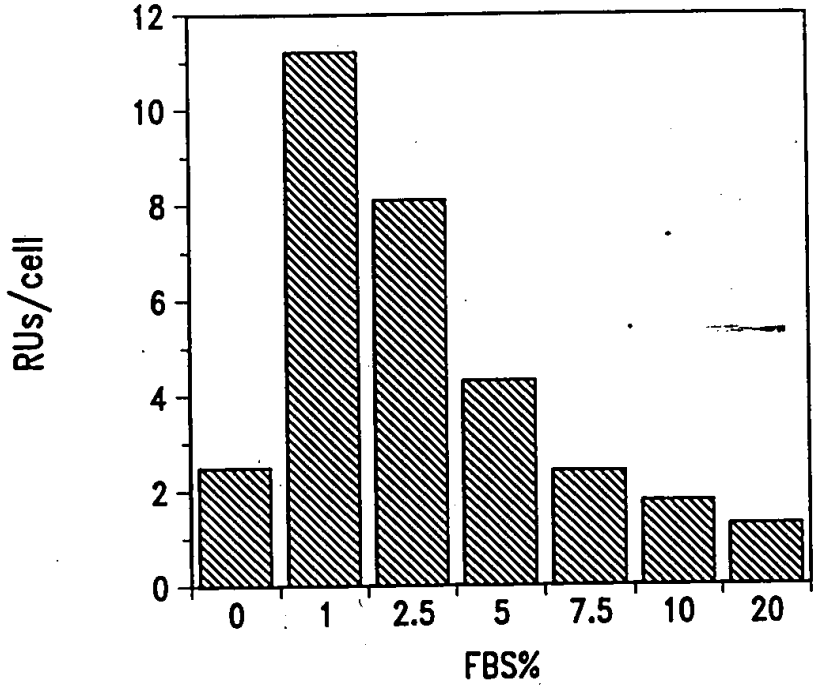

12
10
8
6
4
2
0
RUs/cell
0
1
2.5
5
7.5
10
20
FBS%

Figure 11

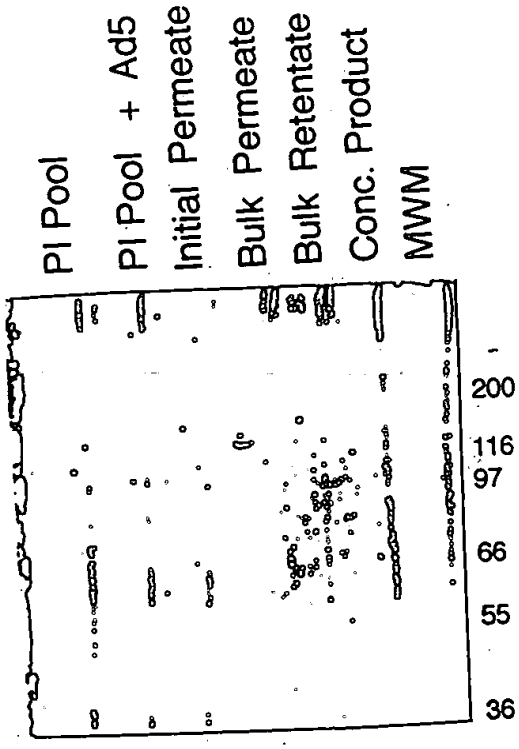

PI Pool
PI Pool + Ad5
Initial Permeate
Bulk Permeate
Bulk Retentate
Conc. Product
MWM
200
116
97
66
55
36

Figure 12

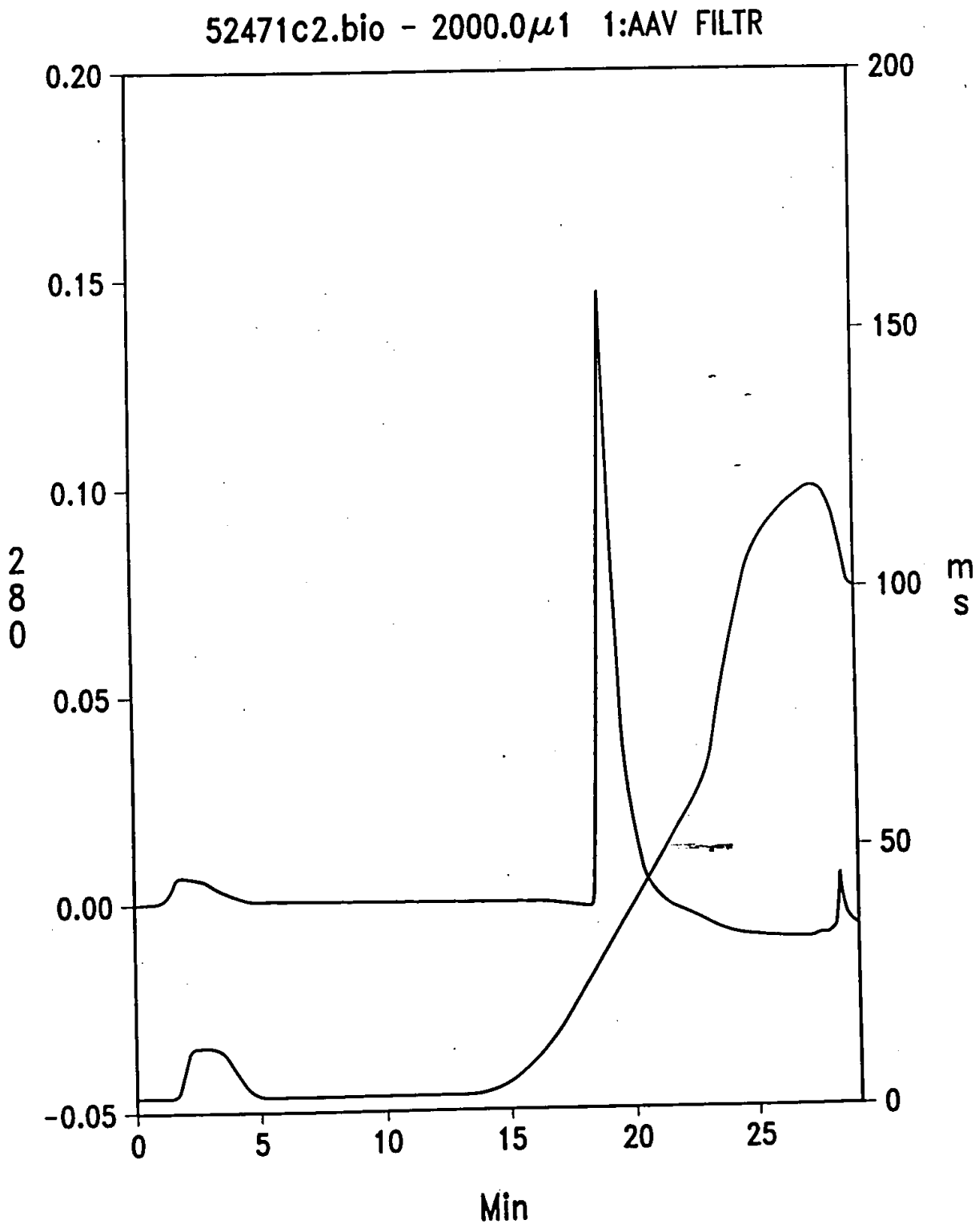
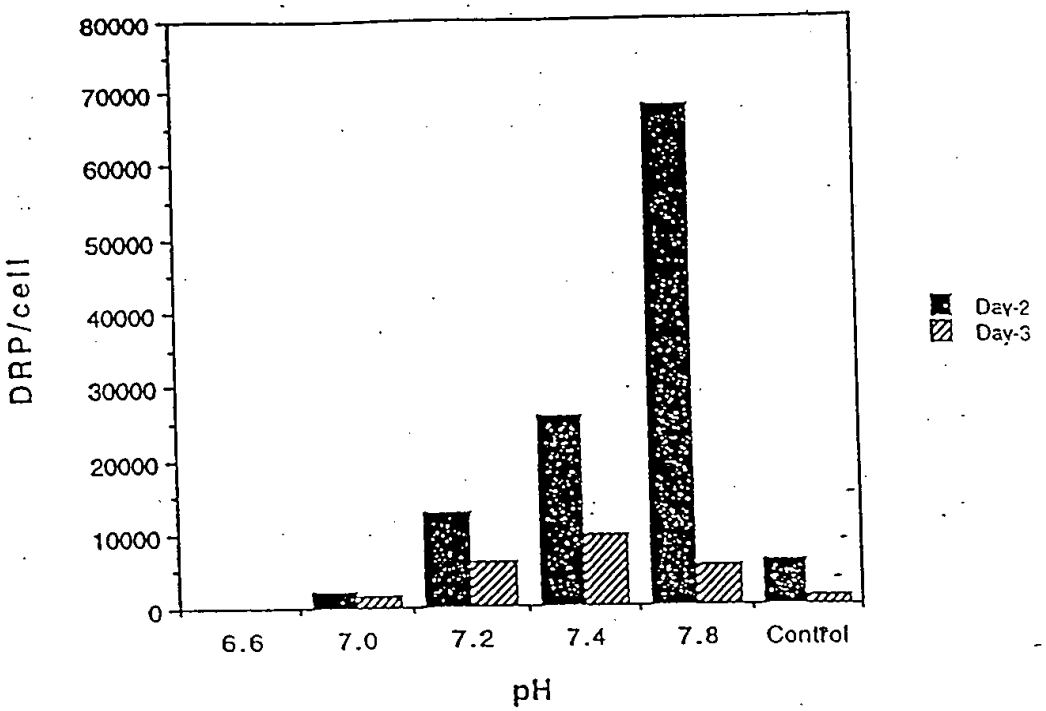

52471c2.bio - 2000.0µl 1:AAV FILTR
0.20
0.15
0.10
0.05
0.00
-0.05
280
200
150
100
50
0
ms
0
5
10
15
20
25
Min

Figure 13

A


pH Experiment #1
DRP Production at different pH's
DRP/cell
80000
70000
60000
50000
40000
30000
20000
10000
0
6.6
7.0
7.2
7.4
7.8
Control
pH
Day-2
Day-3

B

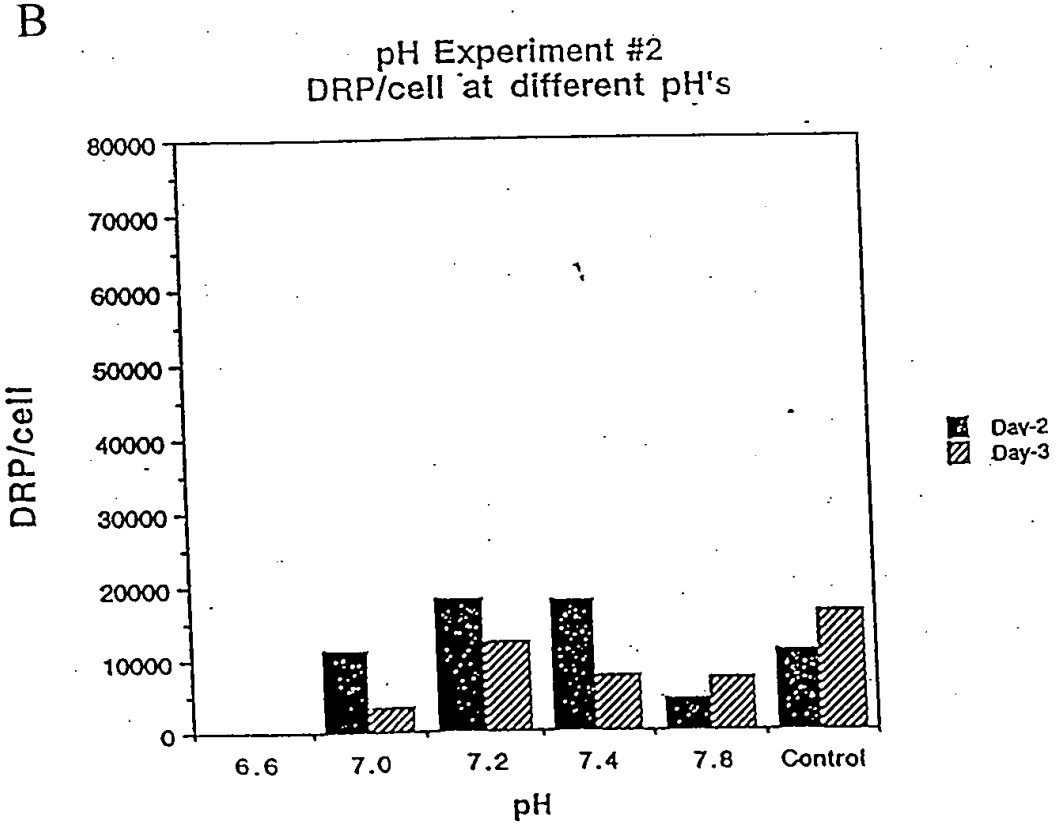
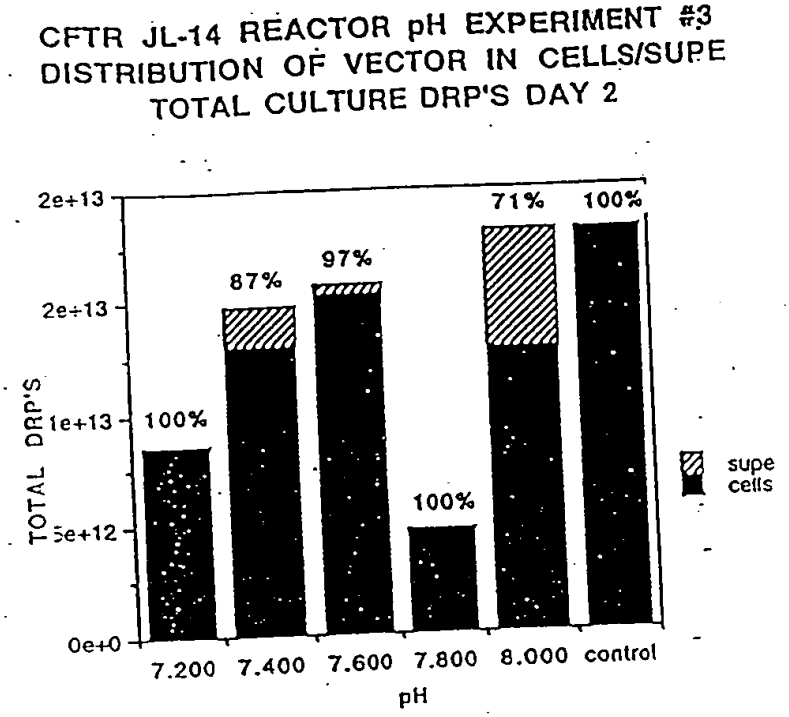

pH Experiment #2
DRP/cell at different pH's
DRP/cell
80000
70000
60000
50000
40000
30000
20000
10000
0
6.6
7.0
7.2
7.4
7.8
Control
pH
Day-2
Day-3

Figure 14

A


CFTR JL-14 REACTOR pH EXPERIMENT #3
DISTRIBUTION OF VECTOR IN CELLS/SUPE
TOTAL CULTURE DRP'S DAY 2
2e+13
2e+13
1e+13
5e+12
0e+0
TOTAL DRP'S
100%
87%
97%
100%
71%
100%
7.200
7.400
7.600
7.800
8.000
control
pH
supe
cells

B

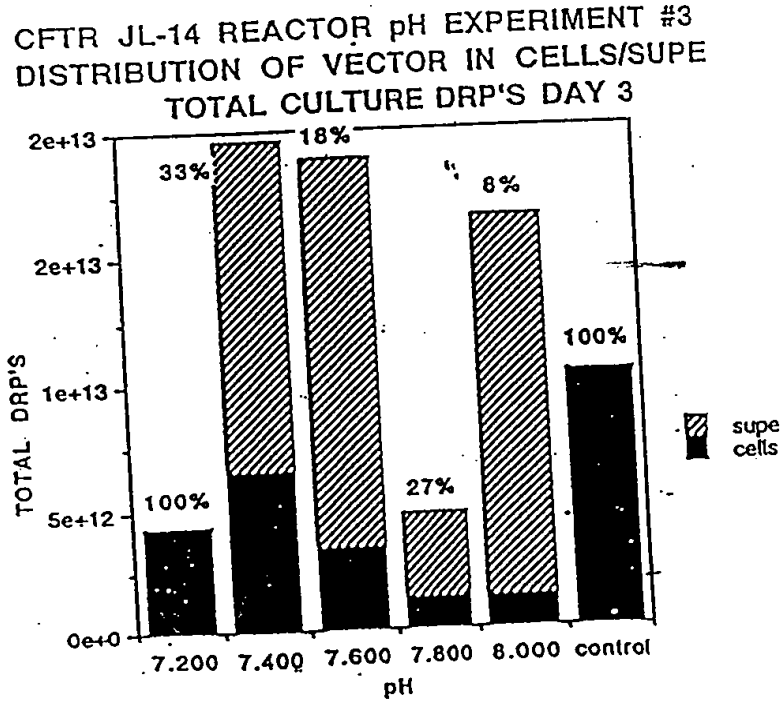
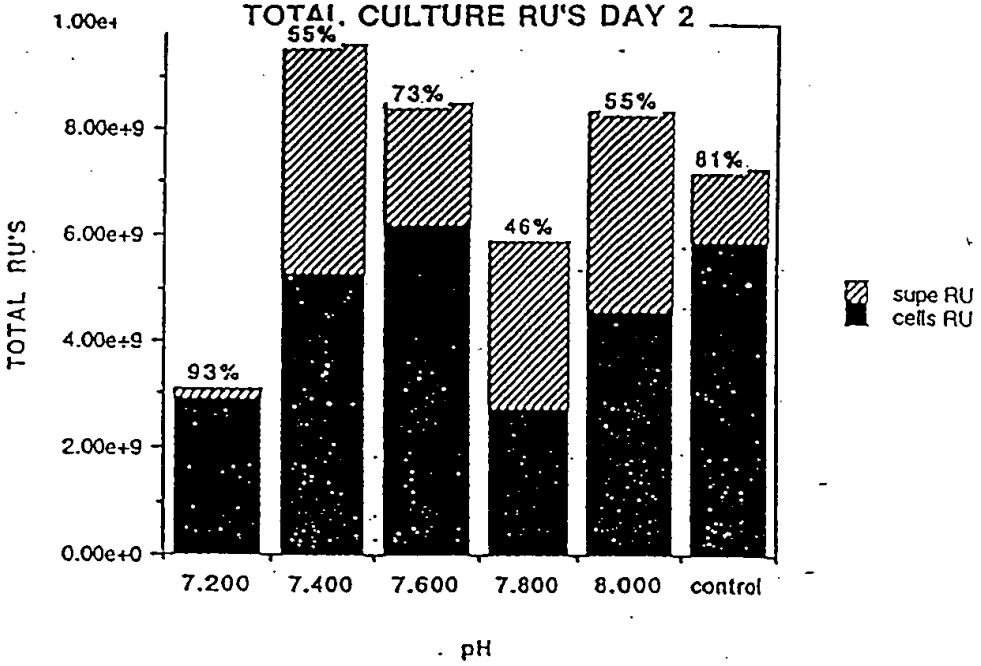

CFTR JL-14 REACTOR pH EXPERIMENT #3
DISTRIBUTION OF VECTOR IN CELLS/SUPE
TOTAL CULTURE DRP'S DAY 3
2e+13
2e+13
1e+13
5e+12
0e+0
TOTAL DRP'S
100%
33%
18%
27%
8%
100%
7.200
7.400
7.600
7.800
8.000
control
pH
supe
cells

Figure 15

A


CFTR JL-14 REACTOR pH EXPERIMENT #3
DISTRIBUTION OF VECTOR IN CELLS/SUPE
TOTAL CULTURE RU'S DAY 2
1.00e+
8.00e+9
6.00e+9
4.00e+9
2.00e+9
0.00e+0
TOTAL RU'S
55%
73%
55%
81%
46%
93%
7.200
7.400
7.600
7.800
8.000
control
pH
supe RU
cells RU

B

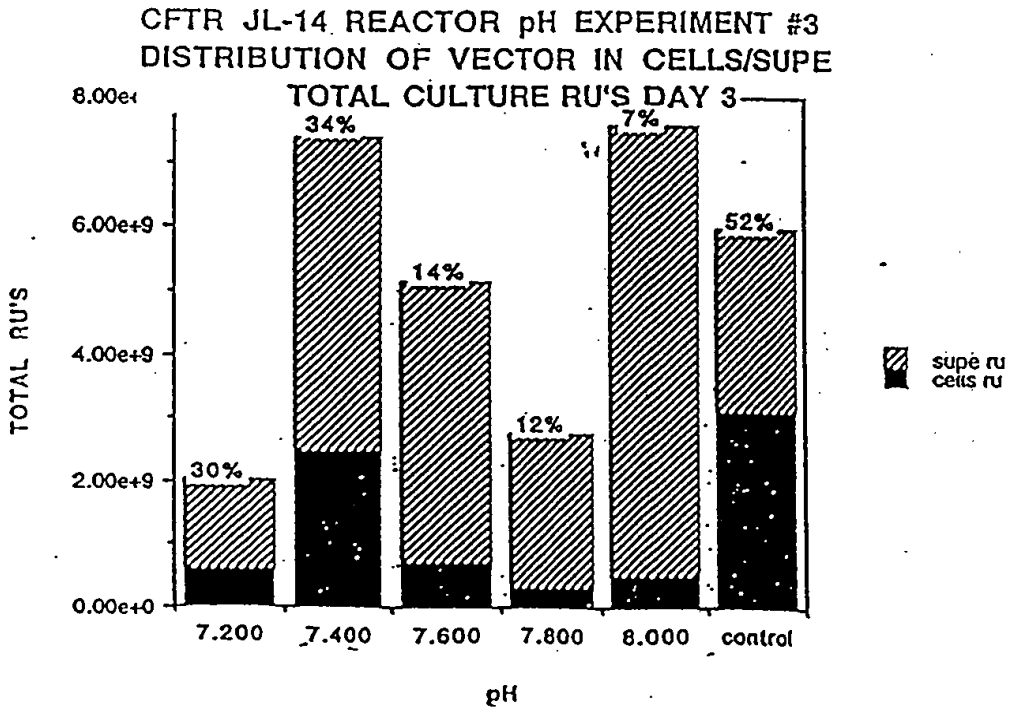

CFTR JL-14 REACTOR pH EXPERIMENT #3
DISTRIBUTION OF VECTOR IN CELLS/SUPE
TOTAL CULTURE RU'S DAY 3
8.00e+
6.00e+9
4.00e+9
2.00e+9
0.00e+0
TOTAL RU'S
34%
7%
52%
14%
12%
30%
7.200
7.400
7.600
7.800
8.000
control
pH
supe ru
cells ru

Figure 16

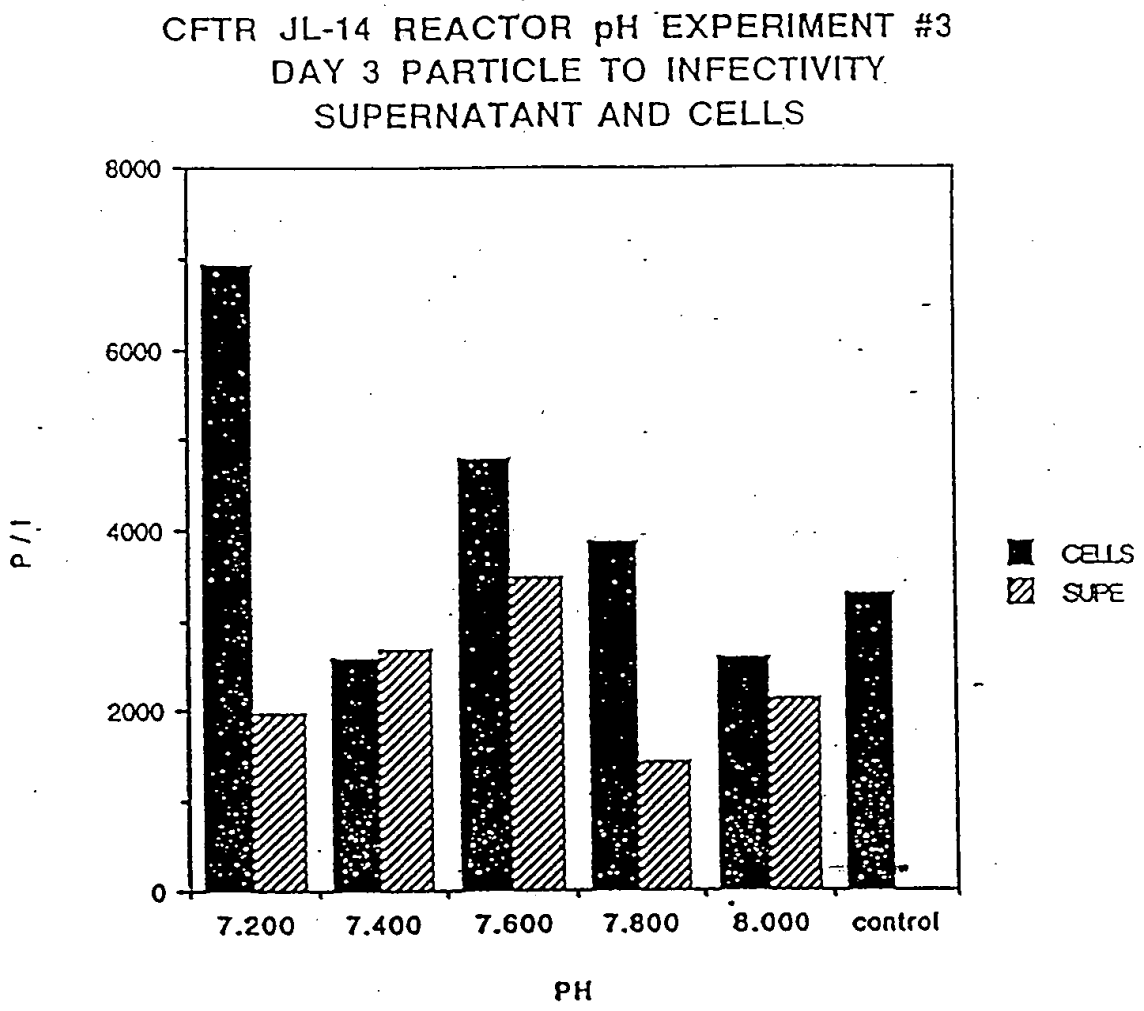

CFTR JL-14 REACTOR pH EXPERIMENT #3
DAY 3 PARTICLE TO INFECTIVITY
SUPERNATANT AND CELLS
8000
6000
4000
2000
0
P / I
7.200
7.400
7.600
7.800
8.000
control
PH
CELLS
SUPE

Figure 17

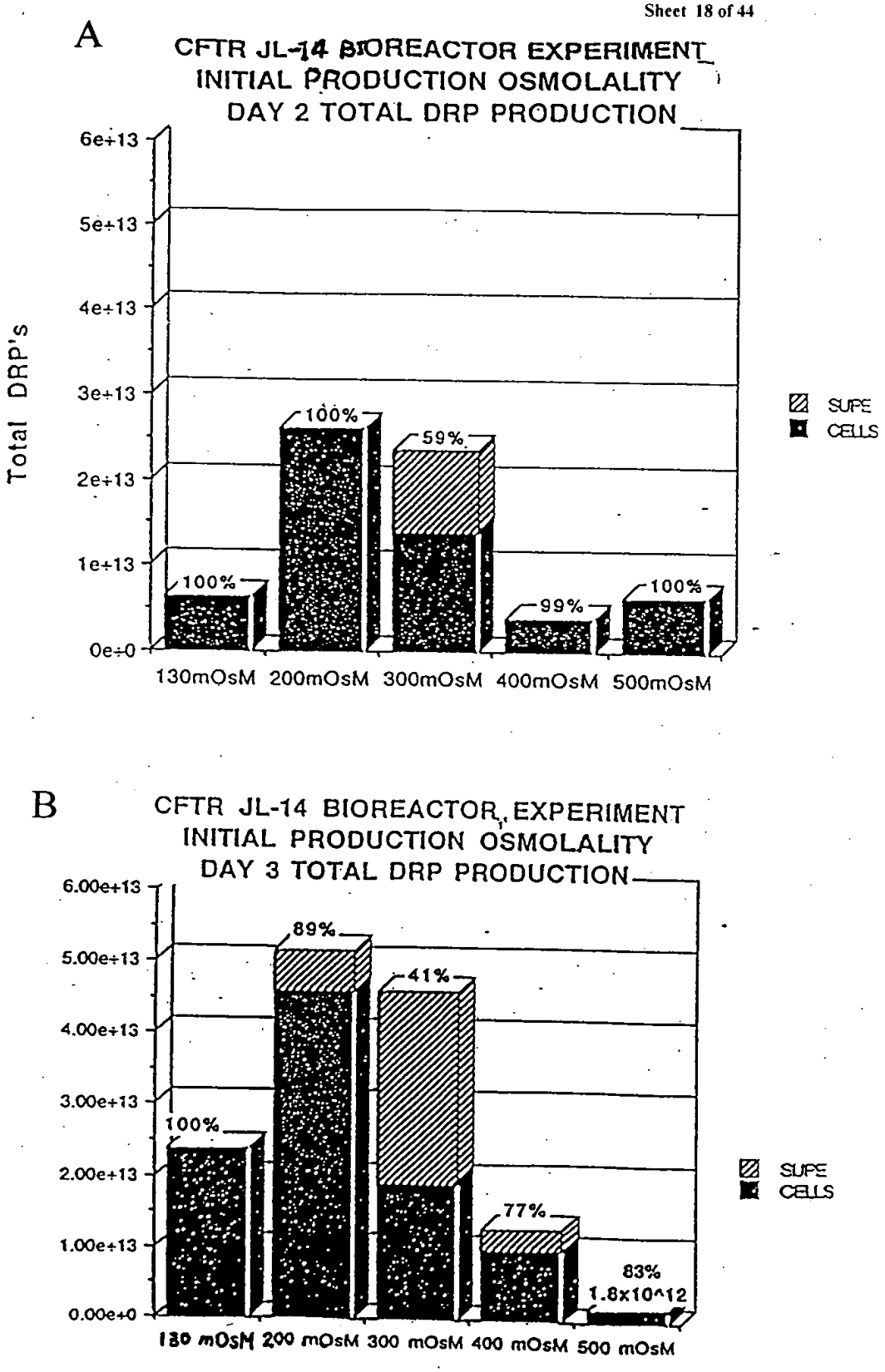

A
CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 2 TOTAL DRP PRODUCTION
Total DRP's
6e+13
5e+13
4e+13
3e+13
2e+13
1e+13
0e+0
100%
100%
59%
99%
100%
130mOsM 200mOsM 300mOsM 400mOsM 500mOsM
SUPE
CELLS
B
CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 3 TOTAL DRP PRODUCTION
TOTAL DRP'S
6.00e+13
5.00e+13
4.00e+13
3.00e+13
2.00e+13
1.00e+13
0.00e+0
100%
89%
41%
77%
83%
1.8x10^12
130 mOsM 200 mOsM 300 mOsM 400 mOsM 500 mOsM
SUPE
CELLS

Figure 18

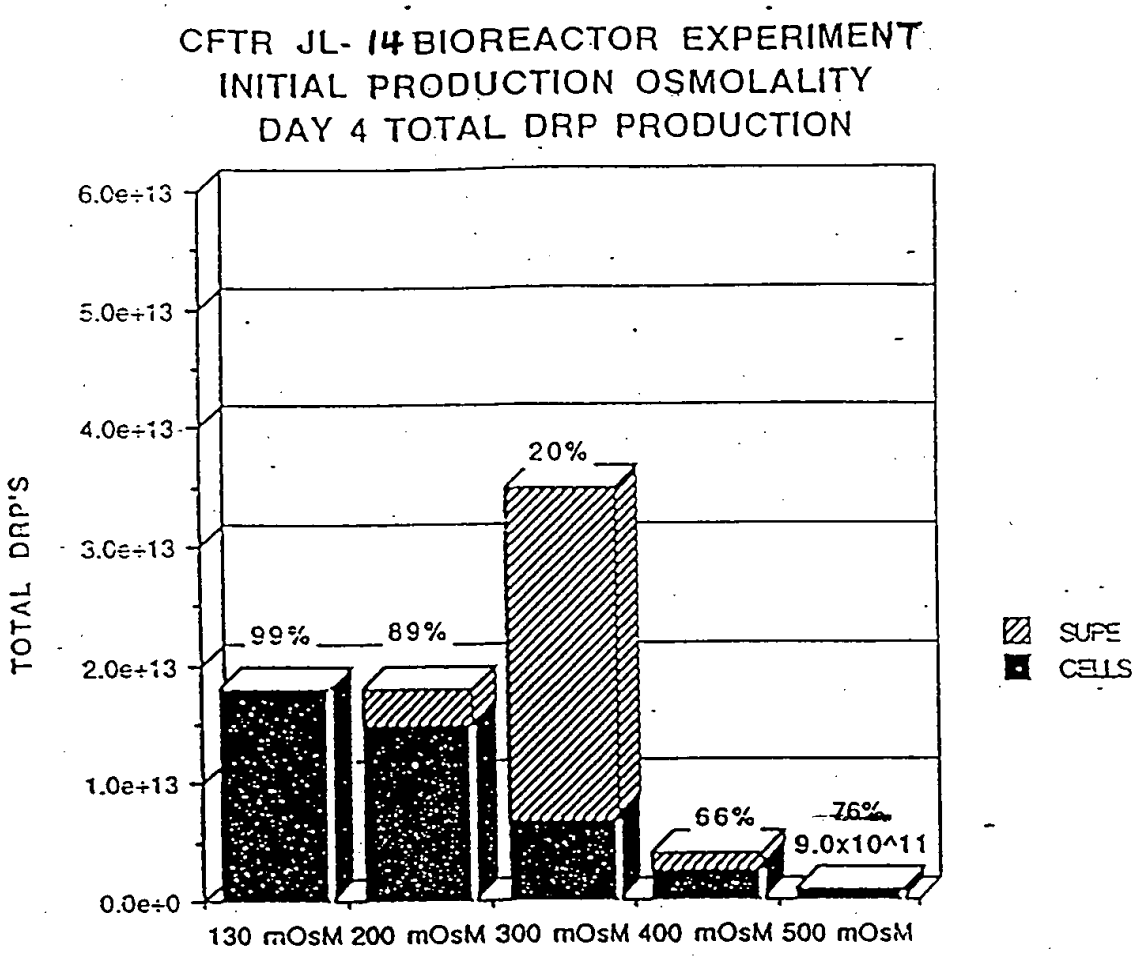
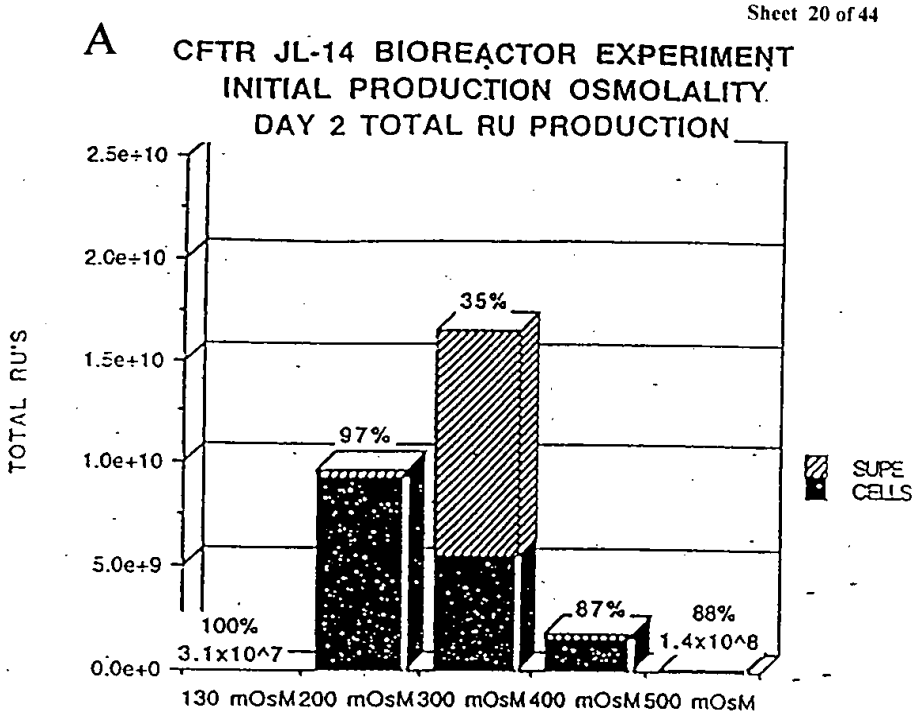

CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 4 TOTAL DRP PRODUCTION
TOTAL DRP'S
6.0e+13
5.0e+13
4.0e+13
3.0e+13
2.0e+13
1.0e+13
0.0e+0
99%
89%
20%
66%
76%
9.0x10^11
130 mOsM
200 mOsM
300 mOsM
400 mOsM
500 mOsM
SUPE
CELLS

Figure 18C


A
CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 2 TOTAL RU PRODUCTION
TOTAL RU'S
2.5e+10
2.0e+10
1.5e+10
1.0e+10
5.0e+9
0.0e+0
35%
97%
100%
3.1x10^7
87%
88%
1.4x10^8
SUPE
CELLS
130 mOsM
200 mOsM
300 mOsM
400 mOsM
500 mOsM

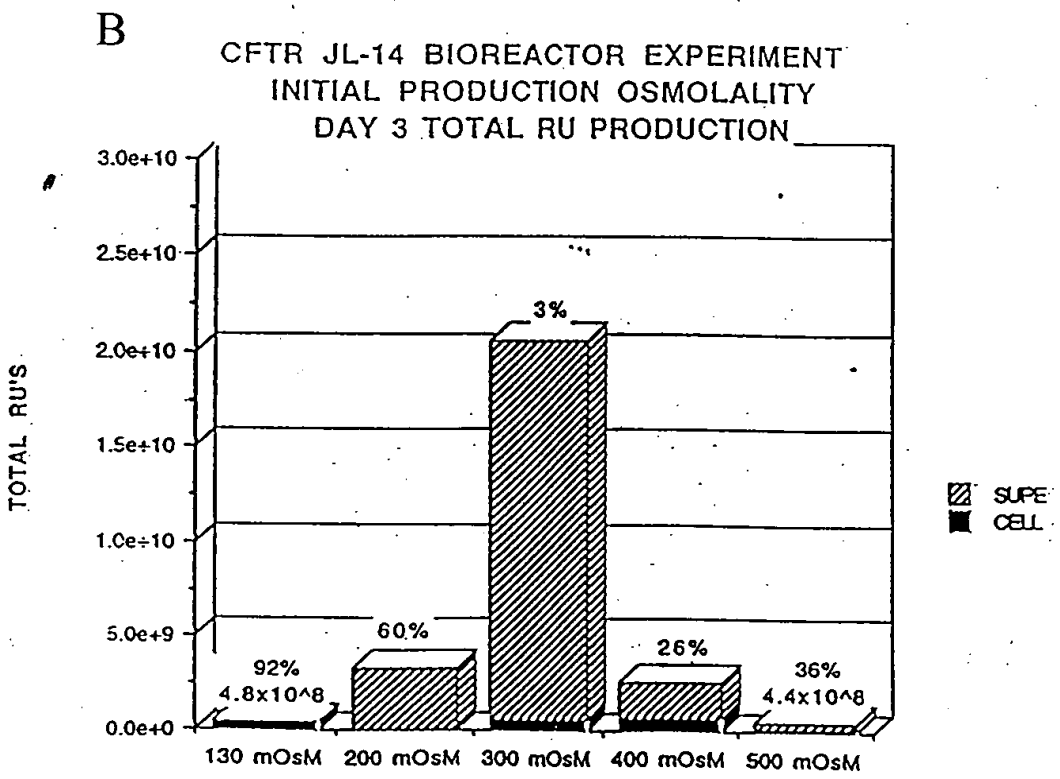

B
CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 3 TOTAL RU PRODUCTION
TOTAL RU'S
3.0e+10
2.5e+10
2.0e+10
1.5e+10
1.0e+10
5.0e+9
0.0e+0
3%
60%
92%
4.8x10^8
26%
36%
4.4x10^8
SUPE
CELL
130 mOsM
200 mOsM
300 mOsM
400 mOsM
500 mOsM

Figure 19

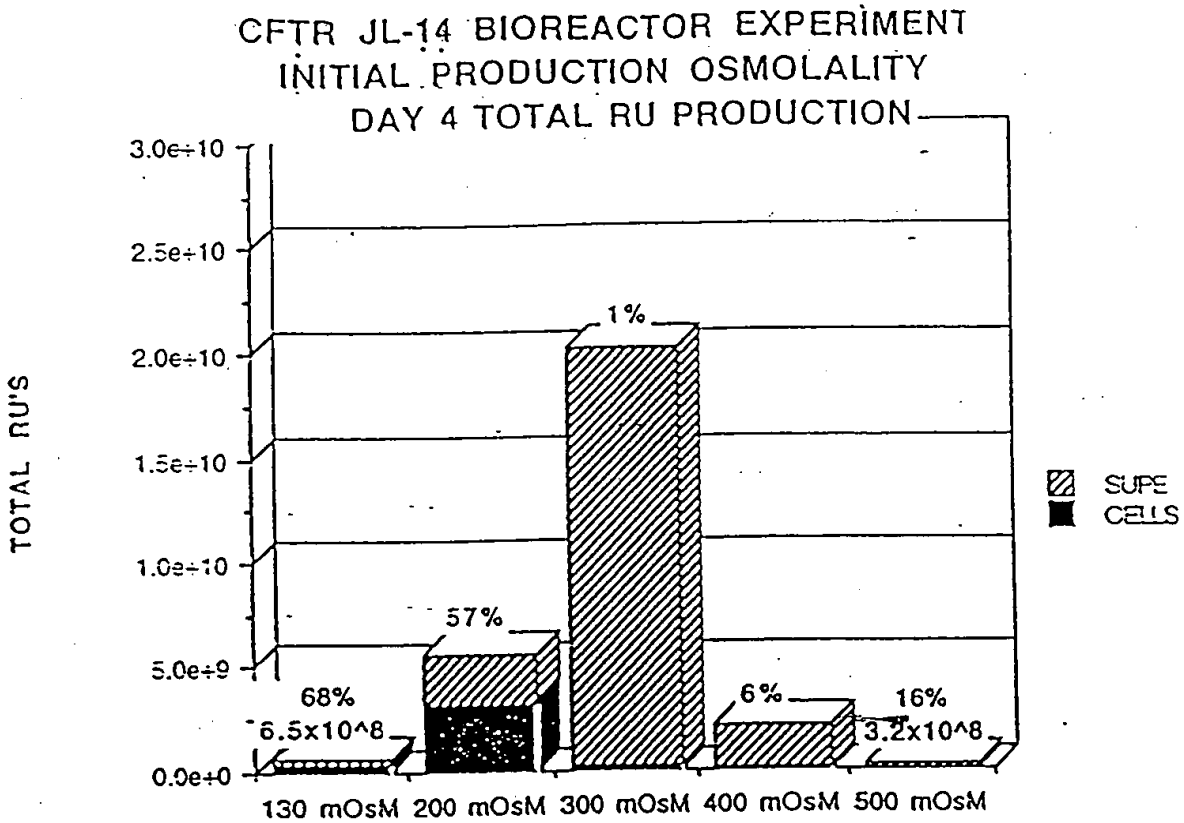

CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
DAY 4 TOTAL RU PRODUCTION
TOTAL RU'S
3.0e+10
2.5e+10
2.0e+10
1.5e+10
1.0e+10
5.0e+9
0.0e+0
68%
6.5x10^8
57%
1%
6%
16%
3.2x10^8
130 mOsM
200 mOsM
300 mOsM
400 mOsM
500 mOsM
SUPE
CELLS

Figure 19C

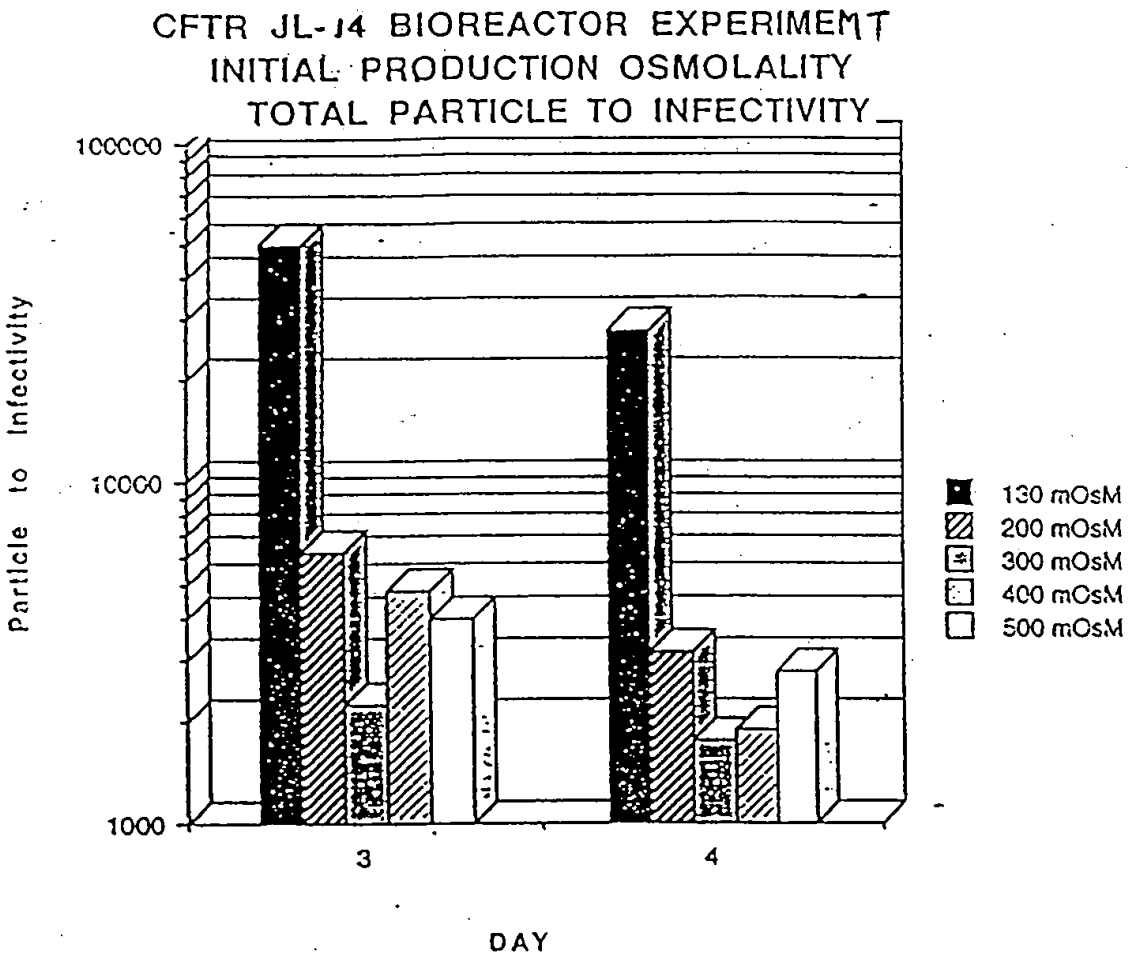
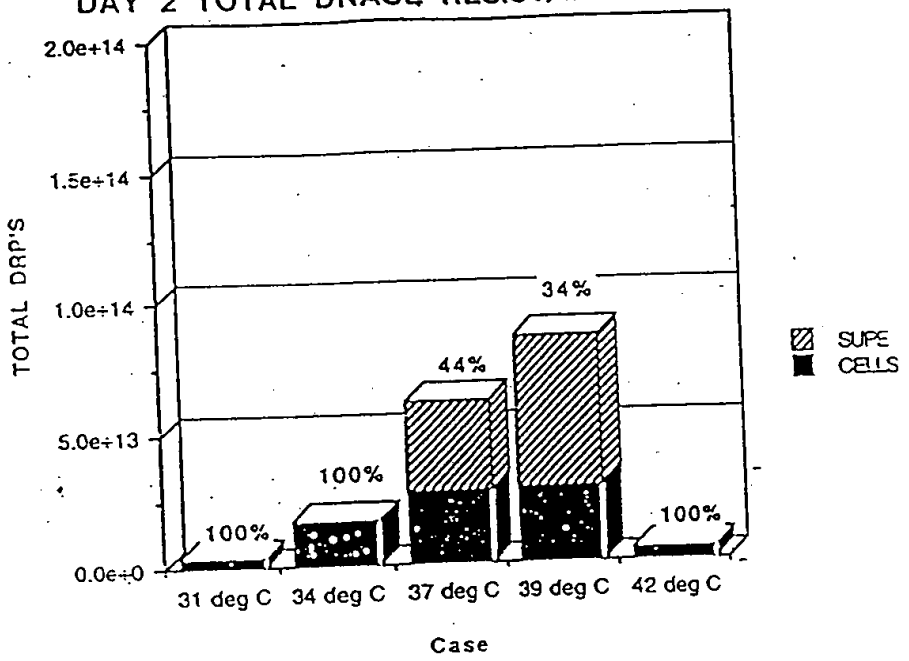

CFTR JL-14 BIOREACTOR EXPERIMENT
INITIAL PRODUCTION OSMOLALITY
TOTAL PARTICLE TO INFECTIVITY
Particle to Infectivity
100000
10000
1000
3
4
DAY
130 mOsM
200 mOsM
300 mOsM
400 mOsM
500 mOsM

Figure 20

A


CFTR JL-14 REACTOR EXP. TEMPERATURE
DAY 2 TOTAL DNASE RESISTANT PARTICLES
TOTAL DRP'S
2.0e+14
1.5e+14
1.0e+14
5.0e+13
0.0e+0
100%
100%
44%
34%
100%
SUPE
CELLS
31 deg C
34 deg C
37 deg C
39 deg C
42 deg C
Case

B

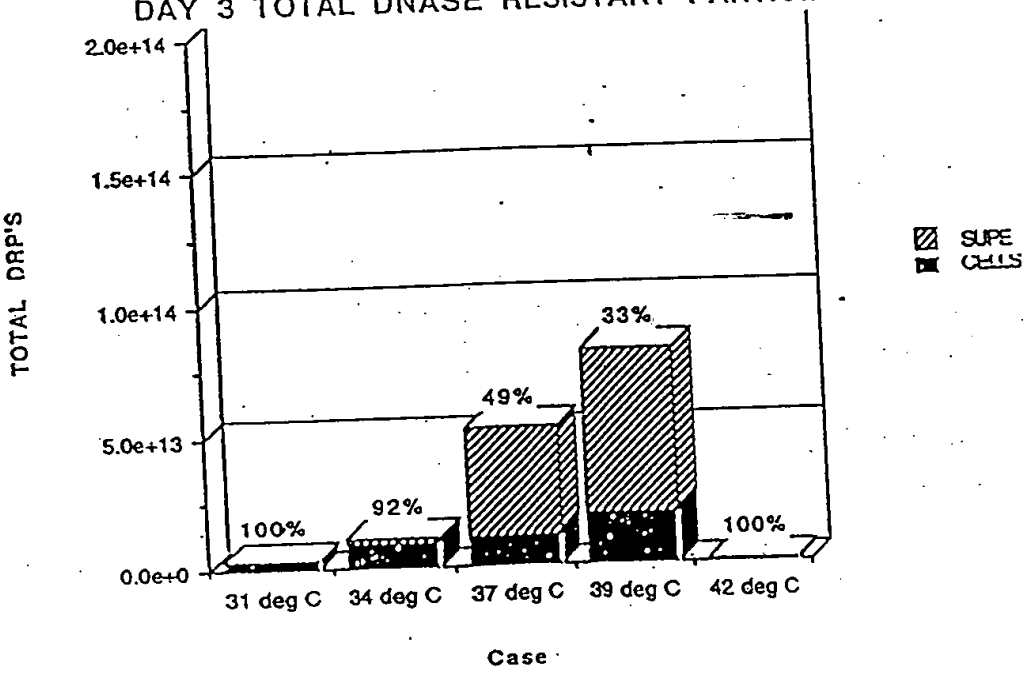

CFTR JL-14 REACTOR EXP. TEMPERATURE
DAY 3 TOTAL DNASE RESISTANT PARTICLES
TOTAL DRP'S
2.0e+14
1.5e+14
1.0e+14
5.0e+13
0.0e+0
100%
92%
49%
33%
100%
SUPE
CELLS
31 deg C
34 deg C
37 deg C
39 deg C
42 deg C
Case

Figure 21

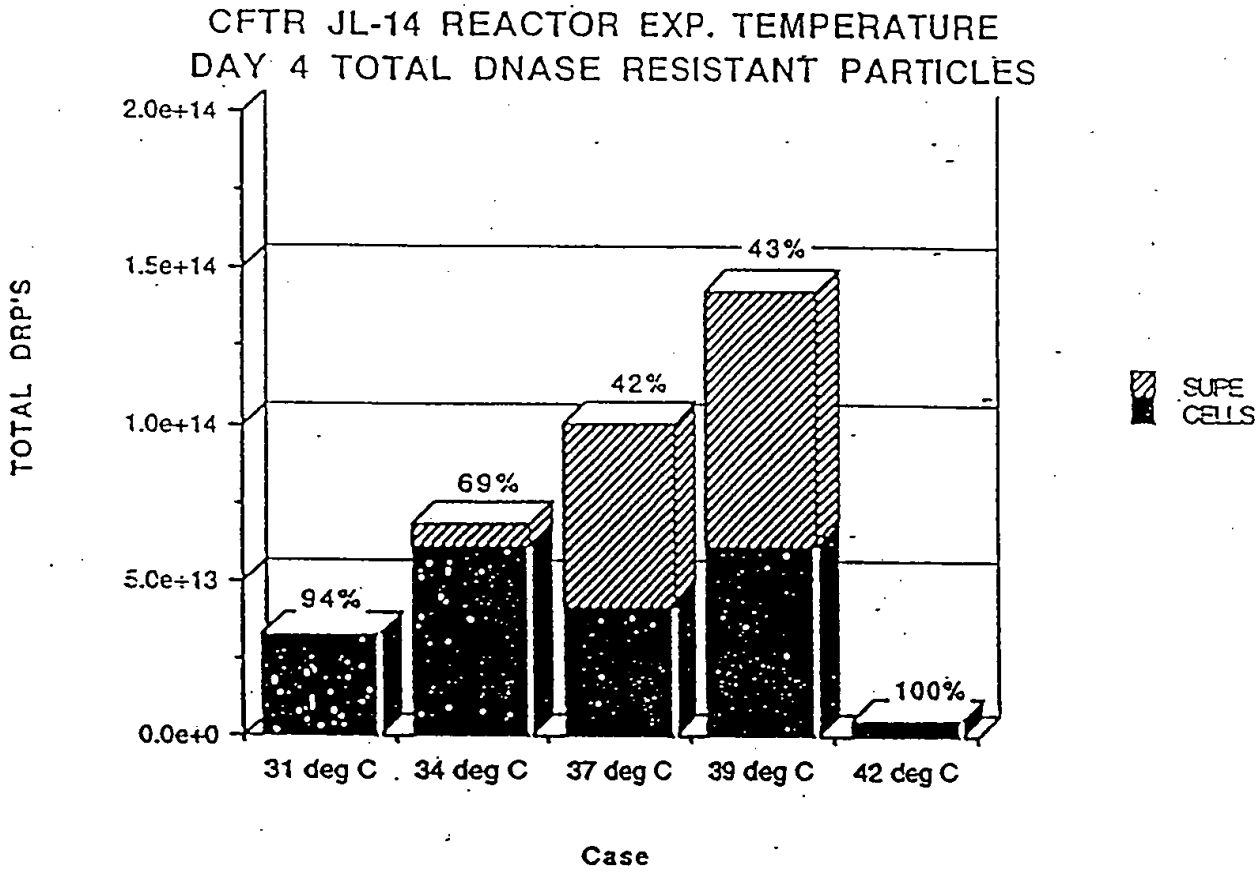

CFTR JL-14 REACTOR EXP. TEMPERATURE
DAY 4 TOTAL DNASE RESISTANT PARTICLES
TOTAL DRP'S
2.0e+14
1.5e+14
1.0e+14
5.0e+13
0.0e+0
94%
69%
42%
43%
100%
31 deg C
34 deg C
37 deg C
39 deg C
42 deg C
Case
SUPE
CELLS

Figure 21C

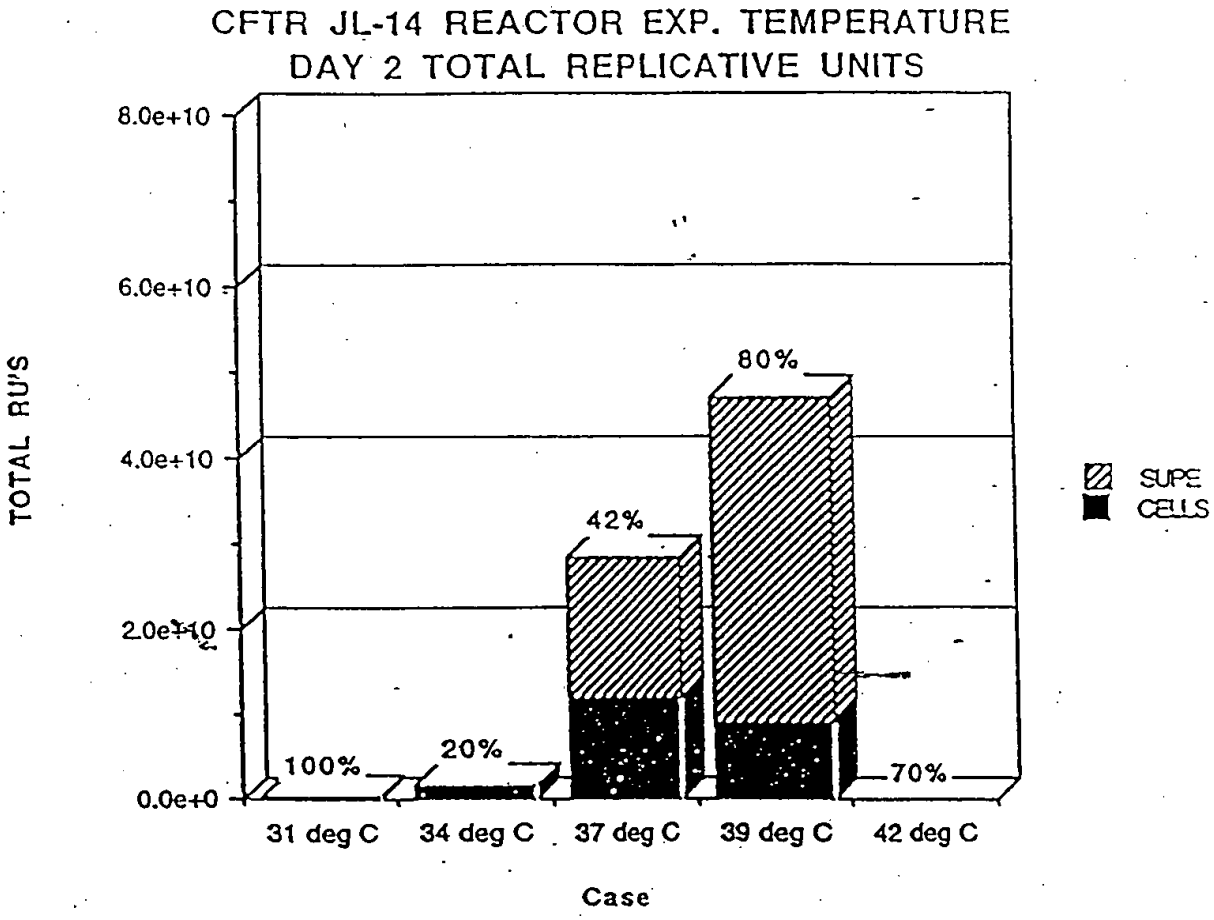
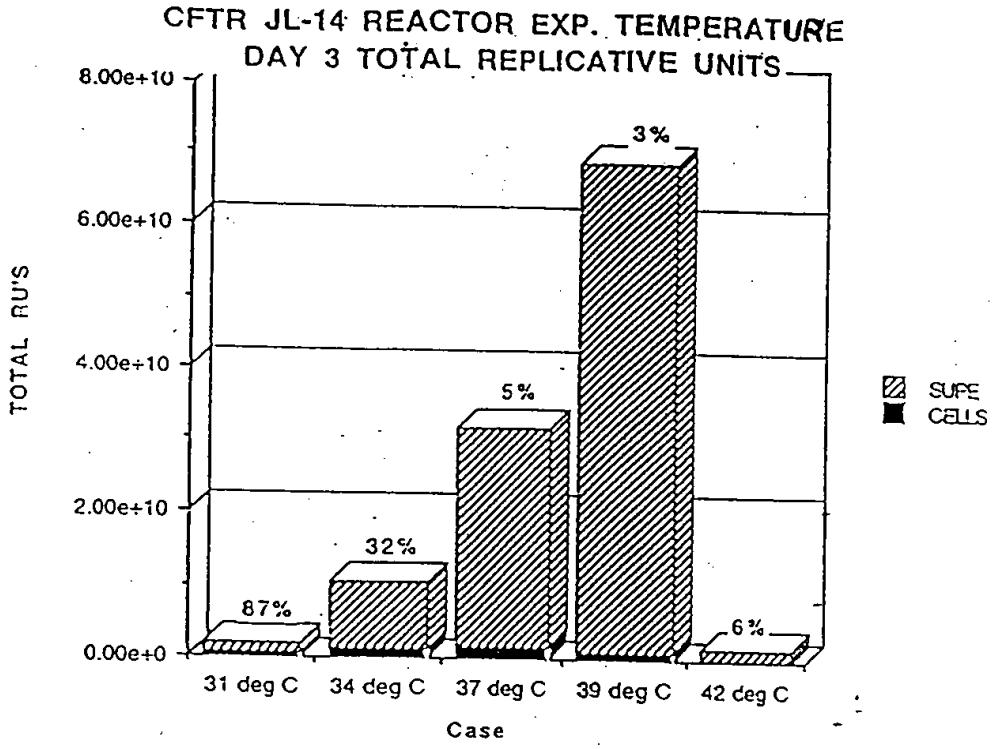
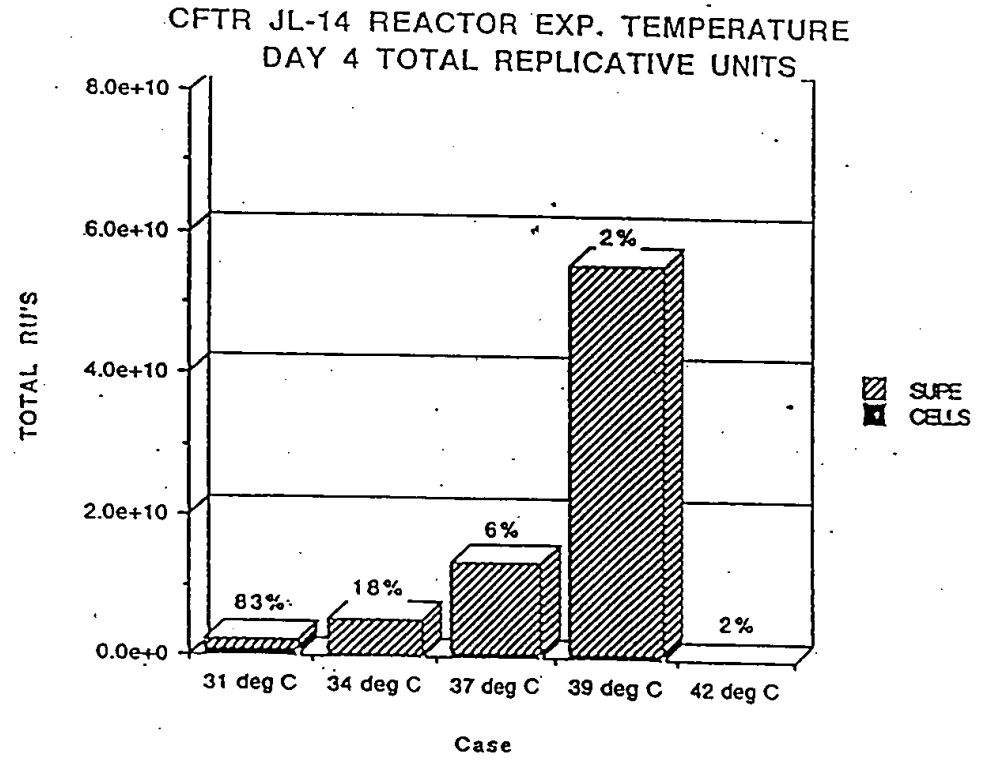

CFTR JL-14 REACTOR EXP. TEMPERATURE
DAY 2 TOTAL REPLICATIVE UNITS
TOTAL RU'S
8.0e+10
6.0e+10
4.0e+10
2.0e+10
0.0e+0
100%
20%
42%
80%
70%
SUPE
CELLS
31 deg C
34 deg C
37 deg C
39 deg C
42 deg C
Case

Figure 22A

B



C



Figures 22B and 22C

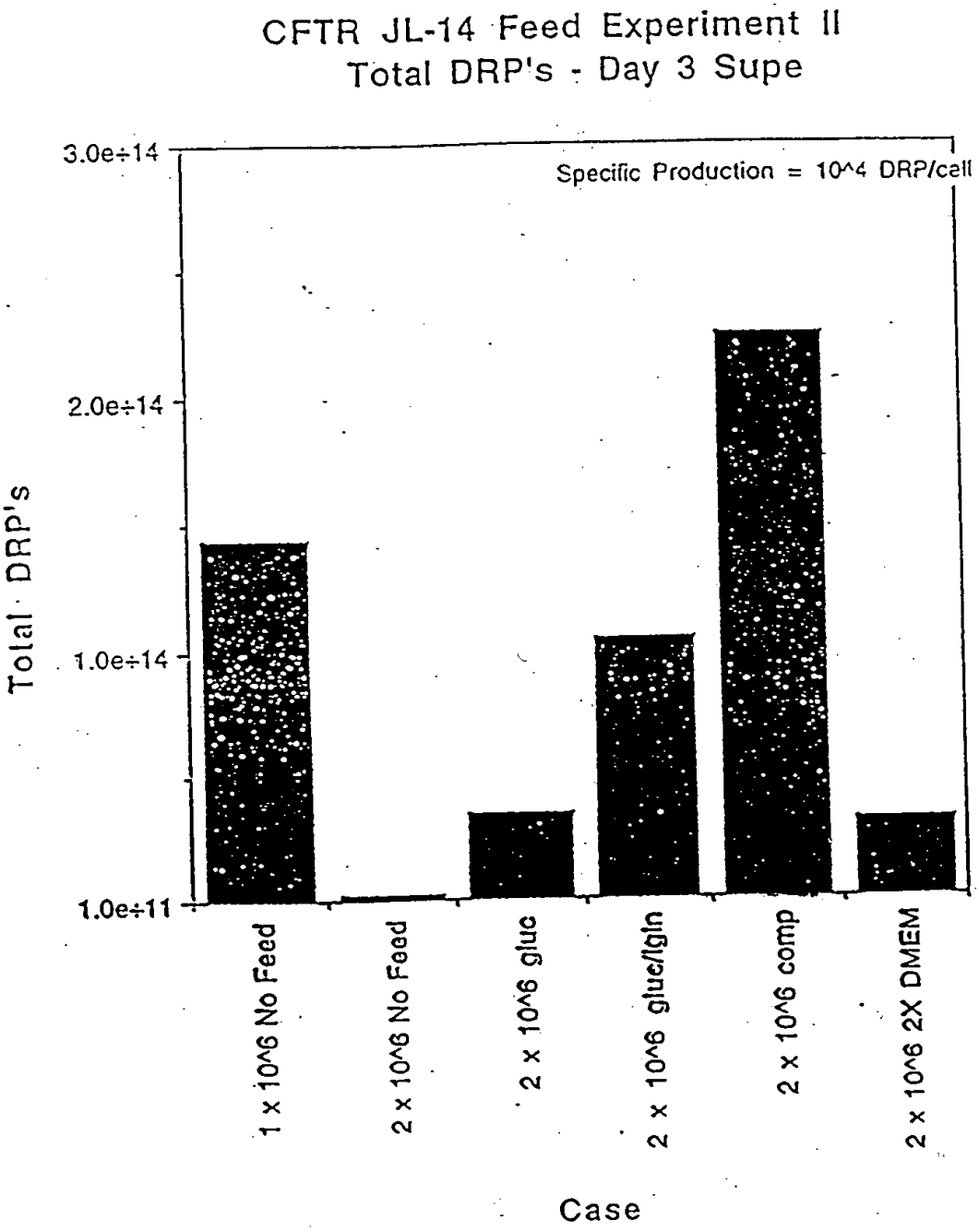

CFTR JL-14 Feed Experiment II
Total DRP's - Day 3 Supe
Specific Production = 10^4 DRP/cell
3.0e+14
2.0e+14
1.0e+14
1.0e+11
Total DRP's
1 x 10^6 No Feed
2 x 10^6 No Feed
2 x 10^6 gluc
2 x 10^6 gluc/gln
2 x 10^6 comp
2 x 10^6 2X DMEM
Case

Figure 23

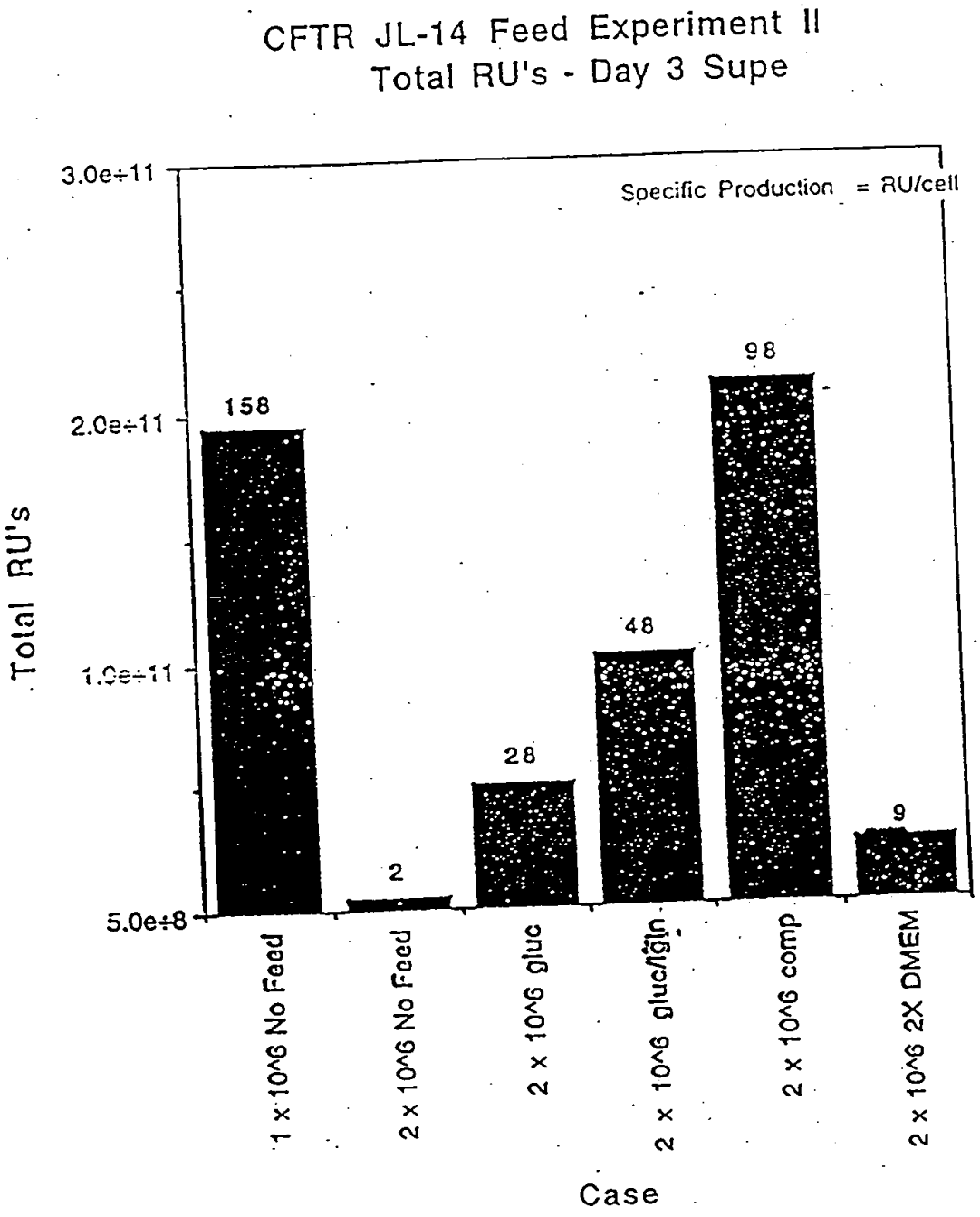

CFTR JL-14 Feed Experiment II
Total RU's - Day 3 Supe
Specific Production = RU/cell
Total RU's
3.0e+11
2.0e+11
1.0e+11
5.0e+8
158
2
28
48
98
9
1 x 10^6 No Feed
2 x 10^6 No Feed
2 x 10^6 gluc
2 x 10^6 gluc/gln
2 x 10^6 comp
2 x 10^6 2X DMEM
Case

Figure 24

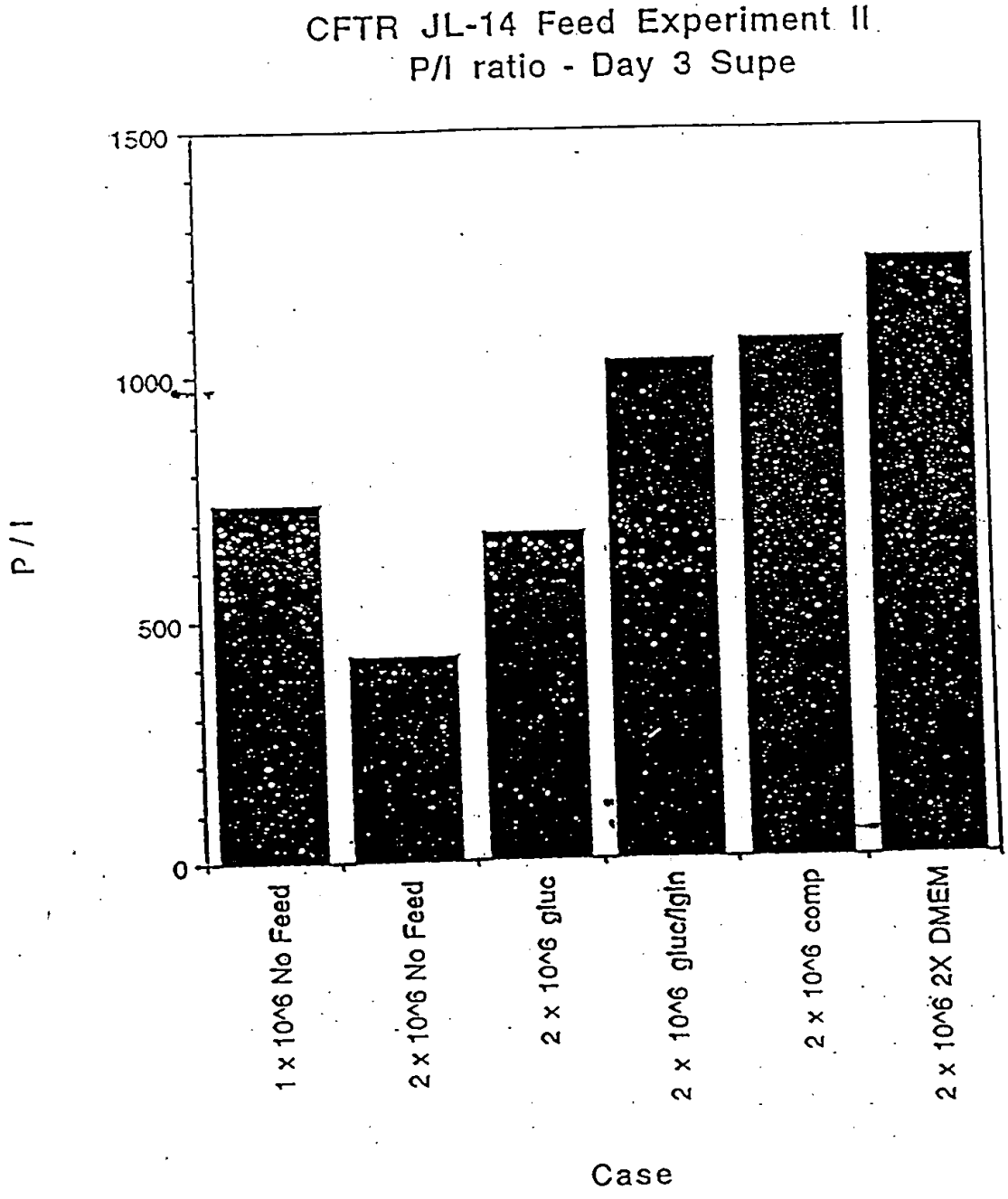

CFTR JL-14 Feed Experiment II
P/I ratio - Day 3 Supe
P / I
1500
1000
500
0
1 x 10^6 No Feed
2 x 10^6 No Feed
2 x 10^6 gluc
2 x 10^6 gluc/gln
2 x 10^6 comp
2 x 10^6 2X DMEM
Case

Figure 25

Lactalbumun Hydrolysate w/Earle's Salts (ELH)		
Base Cat No.	11250	11800
	1XLiquid	Powder
Component	mg/L	mg/L
INORGANIC SALTS:		
$CaCl_2$ (anhyd.)	200.00	200.00
KCl	400.00	400.00
$MgSO_4$ (anhyd.)	97.67	97.70
NaCl	6800.00	6800.00
$NaHCO_3$	2200.00	-
$NaH_2PO_4 \cdot H_2O$	140.00	140.00
OTHER COMPONENTS:		
D-Glucose	1000.00	1000.00
Lactalbumin Hydrolysate	6500.00	5000.00
Phenol Red	10.00	10.00

MEM Amino Acids Solutions[2]		
Base Cat No.	11136	21135
Component	50X Liquid	50X Liquid
AMINO ACIDS:	mg/L	mg/L
L-Arginine	6320.00	6320.00
L-Cystine	1200.00	1200.00
L-Glutamine	-	14600.00
L-Histidine-HCl-H_2O	2100.00	2100.00
L-Isoleucine	2625.00	2625.00
L-Luecine	2620.00	2620.00
L-Lysins HCl	3625.00	3625.00
L-Methionine	755.00	755.00
L-Phenylalnine	1650.00	1650.00
L-Threonine	2380.00	2380.00
L-Tryptophan	510.00	510.00
L-Tyrosine	1800.00	1800.00
L-Valine	2340.00	2340.00

References:
1. Eagle, H. (1955) Proc. Soc. Exp. Biol. Med. 89, 362.
2. Eagle, H. (1959) Science 130, 432

MEM Non-Essential Amino Acids Solution[2]	
Base Cat No.	11140
	100X
	Liquid
Component	mg/L
AMINO ACIDS:	
L-Algnine	890.00
L-Asparagine	1500.00
L-Aspartic	1330.00
L-Glutamine	1470.00
Glycine	750.00
L-Proline	1150.00
L-Serine	1050.00

MEM Vitamon Solutions[2]	
Base Cat No.	11120
	50X Liquid
Component	mg/L
NaCl	8500.00
D-Ca Pantothenate	100.00
Choline Chloride	100.00
Folic Acid	100.00
I-Inositol	200.00
Nicotinamide	100.00
Pyridoxal-HCl	100.00
Riboflavin	10.00
Thiamine HCl	100.00

Figure 26

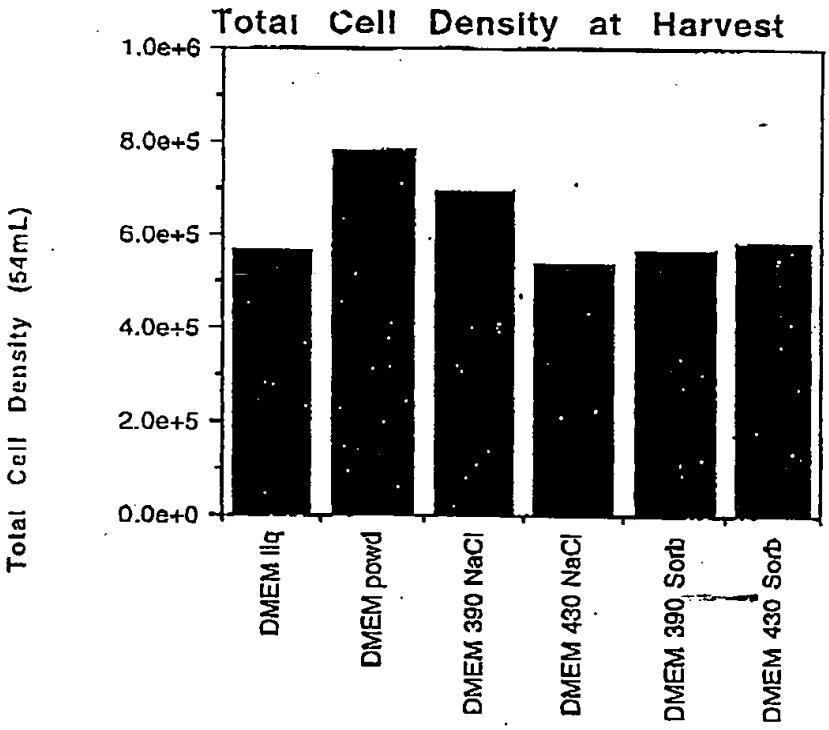

Total Cell Density at Harvest
Total Cell Density (54mL)
1.0e+6
8.0e+5
6.0e+5
4.0e+5
2.0e+5
0.0e+0
DMEM liq
DMEM powd
DMEM 390 NaCl
DMEM 430 NaCl
DMEM 390 Sorb
DMEM 430 Sorb

Figure 27

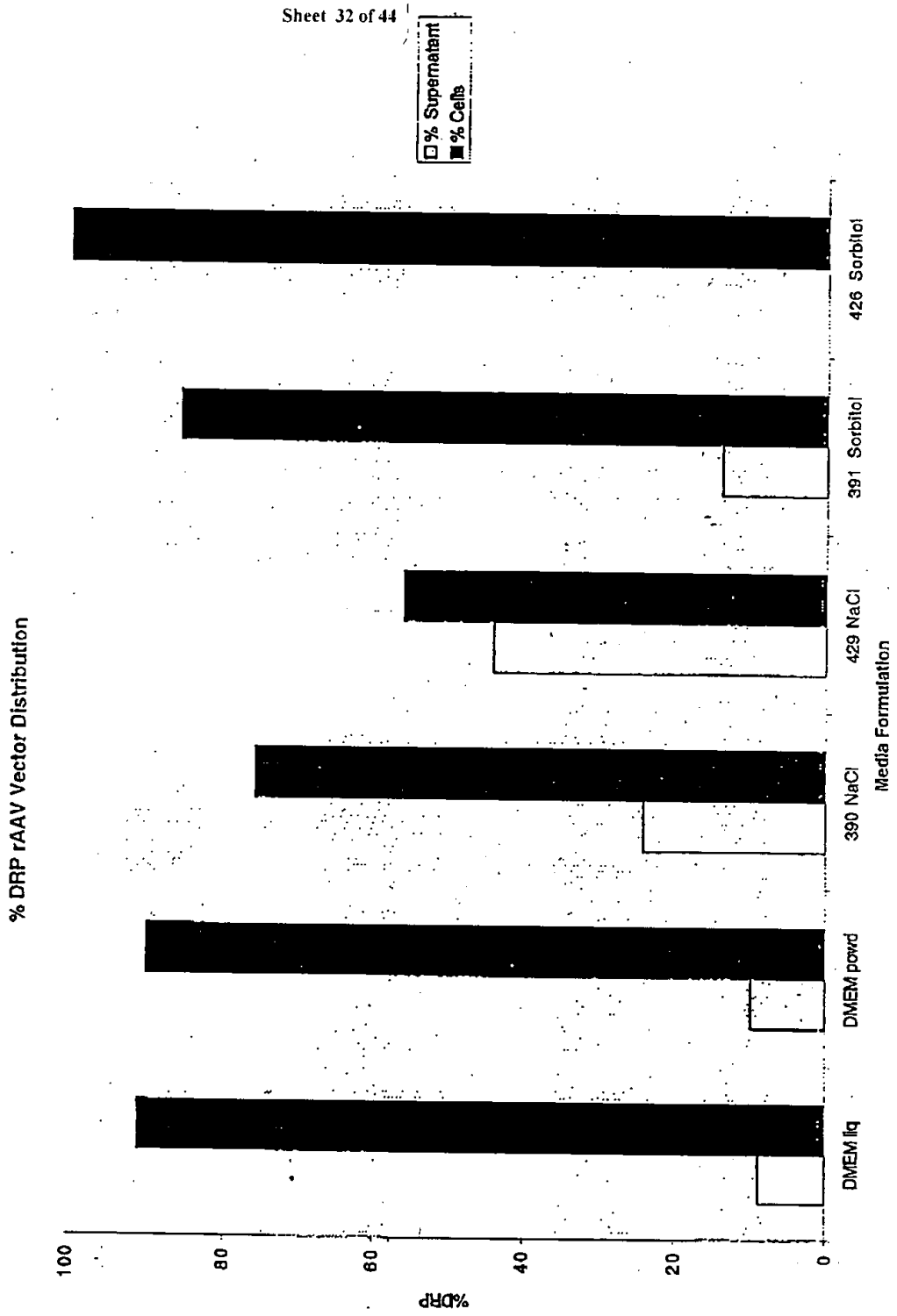

% Supernatant
% Cells
% DRP rAAV Vector Distribution
426 Sorbitol
391 Sorbitol
429 NaCl
390 NaCl
DMEM powd
DMEM liq
Media Formulation
100
80
60
40
20
0
%DRP

Figure 28

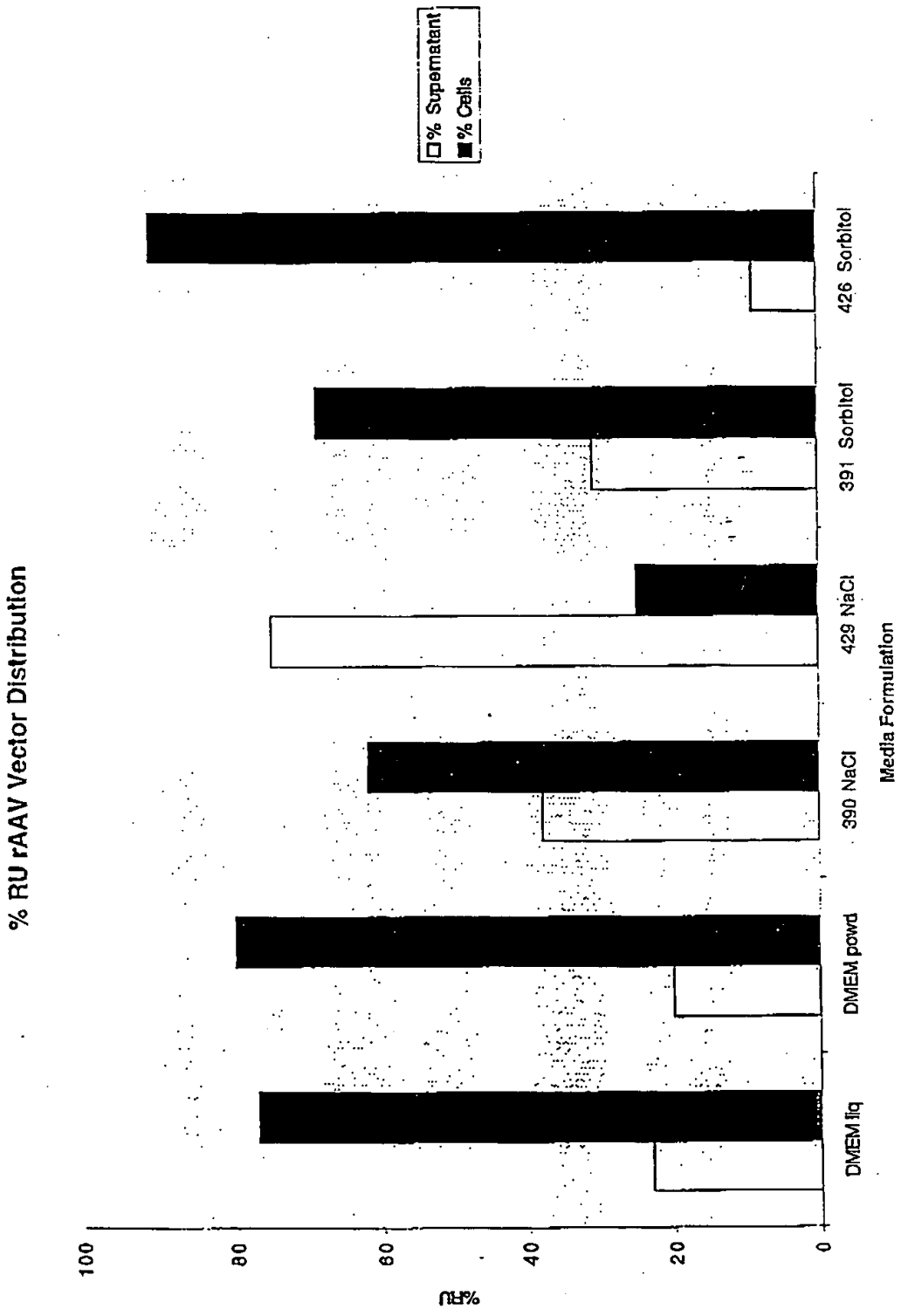

% Supernatant
% Cells
% RU rAAV Vector Distribution
426 Sorbitol
391 Sorbitol
429 NaCl
390 NaCl
DMEM powd
DMEM liq
Media Formulation
100
80
60
40
20
0
%RU

Figure 29

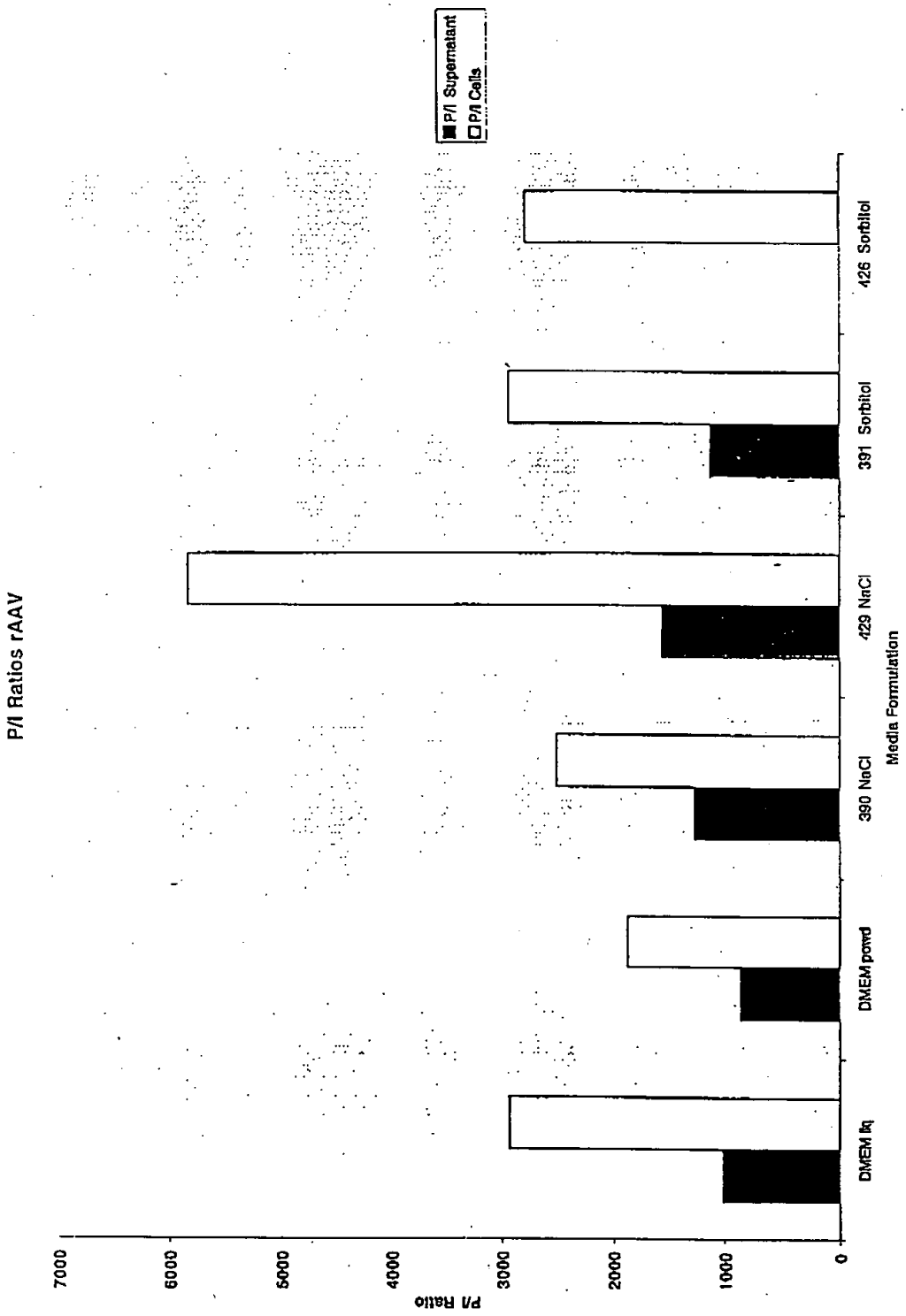
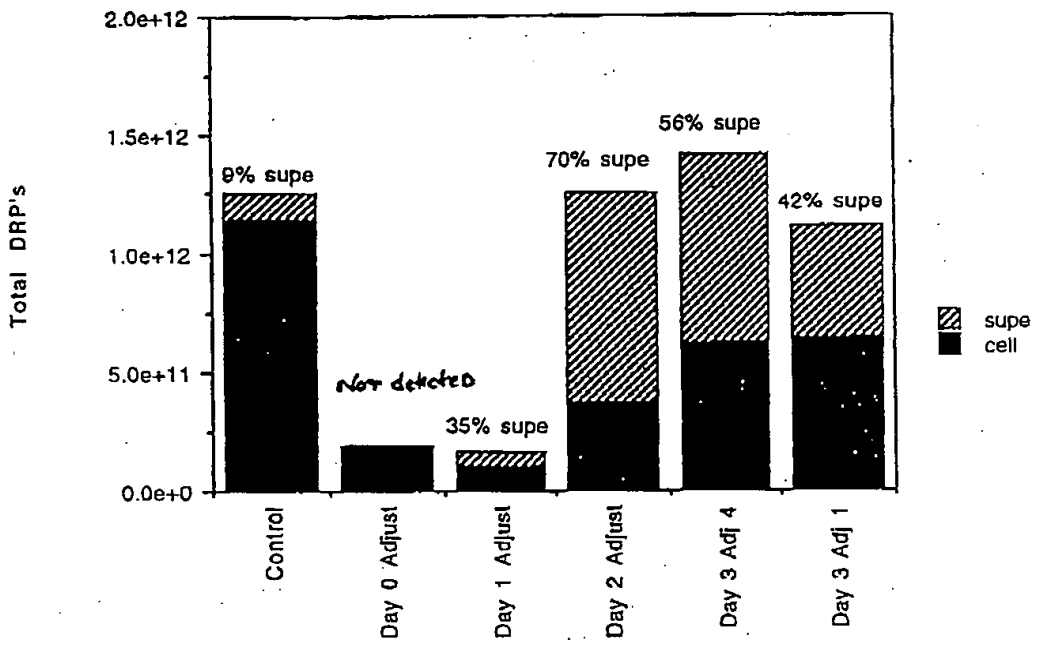

P/I Supernatant
P/I Cells
P/I Ratios rAAV
P/I Ratio
7000
6000
5000
4000
3000
2000
1000
0
426 Sorbitol
391 Sorbitol
429 NaCl
390 NaCl
DMEM powd
DMEM liq
Media Formulation

Figure 30

A


Daily Salt Adjustment T-Flask
Total DRP's with Cell and Sup Dist.
Total DRP's
2.0e+12
1.5e+12
1.0e+12
5.0e+11
0.0e+0
9% supe
Not detected
35% supe
70% supe
56% supe
42% supe
Control
Day 0 Adjust
Day 1 Adjust
Day 2 Adjust
Day 3 Adj 4
Day 3 Adj 1
supe
cell

B

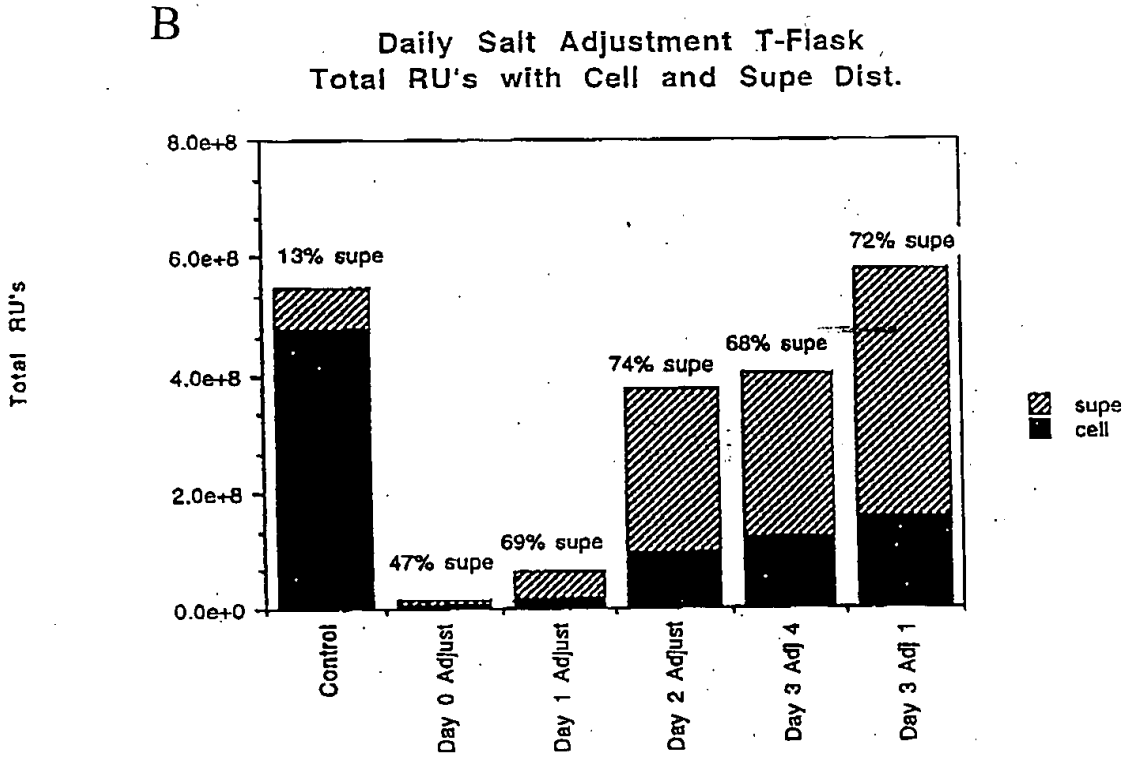

Daily Salt Adjustment T-Flask
Total RU's with Cell and Supe Dist.
Total RU's
8.0e+8
6.0e+8
4.0e+8
2.0e+8
0.0e+0
13% supe
47% supe
69% supe
74% supe
68% supe
72% supe
Control
Day 0 Adjust
Day 1 Adjust
Day 2 Adjust
Day 3 Adj 4
Day 3 Adj 1
supe
cell

Figure 31

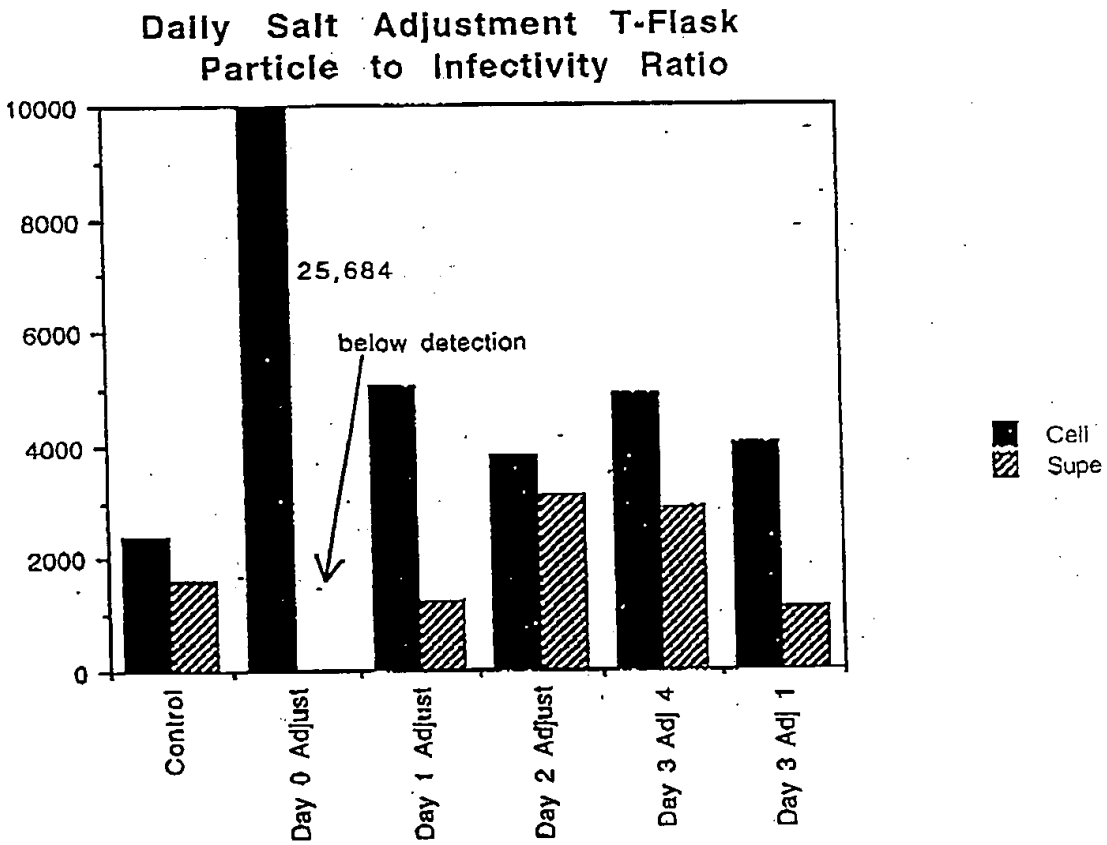
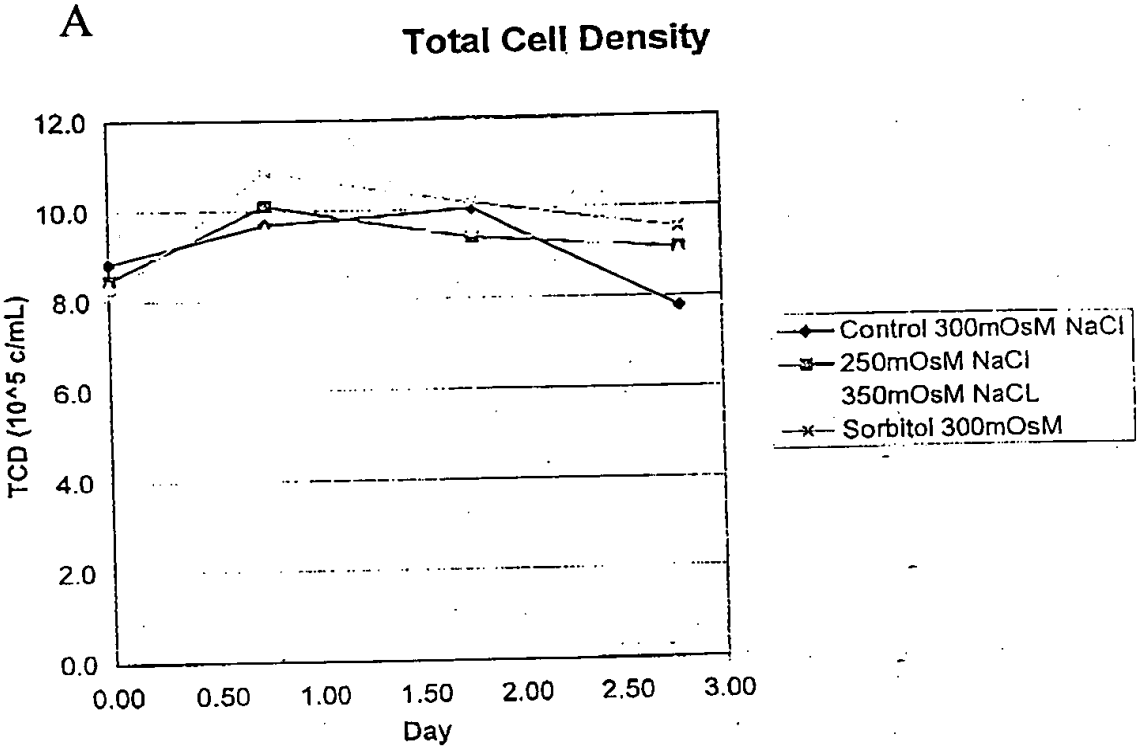

Daily Salt Adjustment T-Flask
Particle to Infectivity Ratio
P/I Ratio
10000
8000
6000
4000
2000
0
25,684
below detection
Control
Day 0 Adjust
Day 1 Adjust
Day 2 Adjust
Day 3 Adj 4
Day 3 Adj 1
Cell
Supe

Figure 32

A


Total Cell Density
TCD (10^5 c/mL)
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0.00
0.50
1.00
1.50
2.00
2.50
3.00
Day
Control 300mOsM NaCl
250mOsM NaCl
350mOsM NaCL
Sorbitol 300mOsM

B

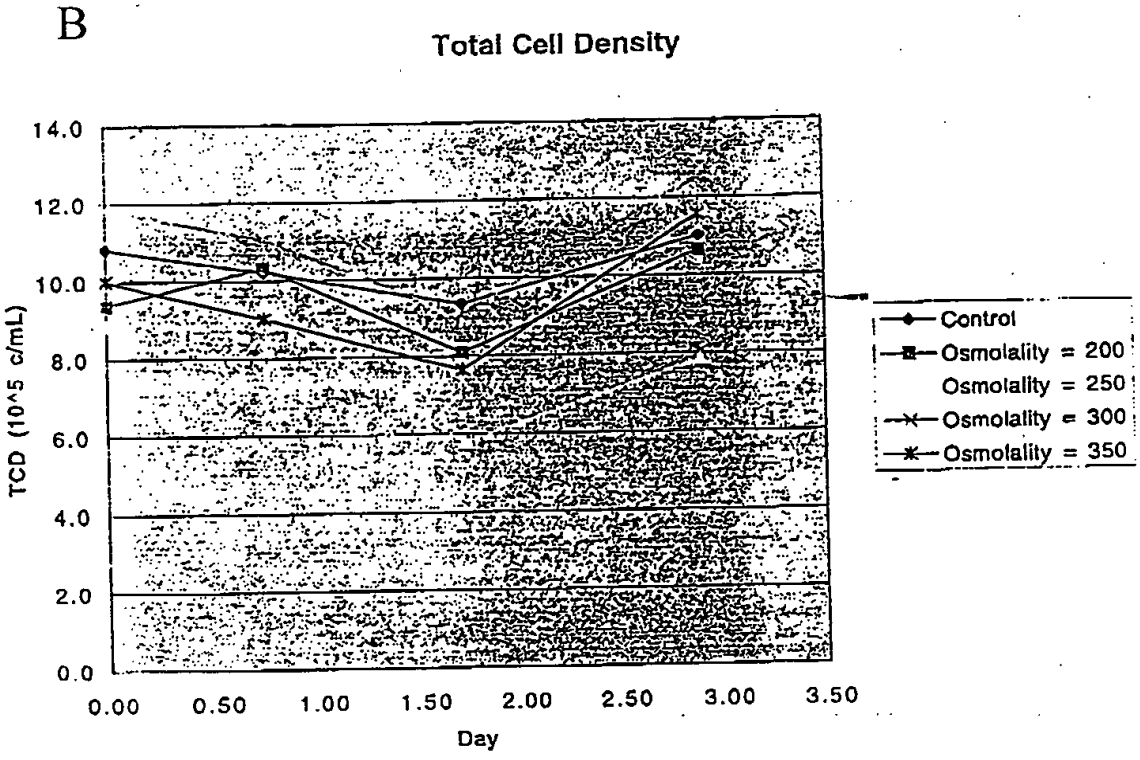
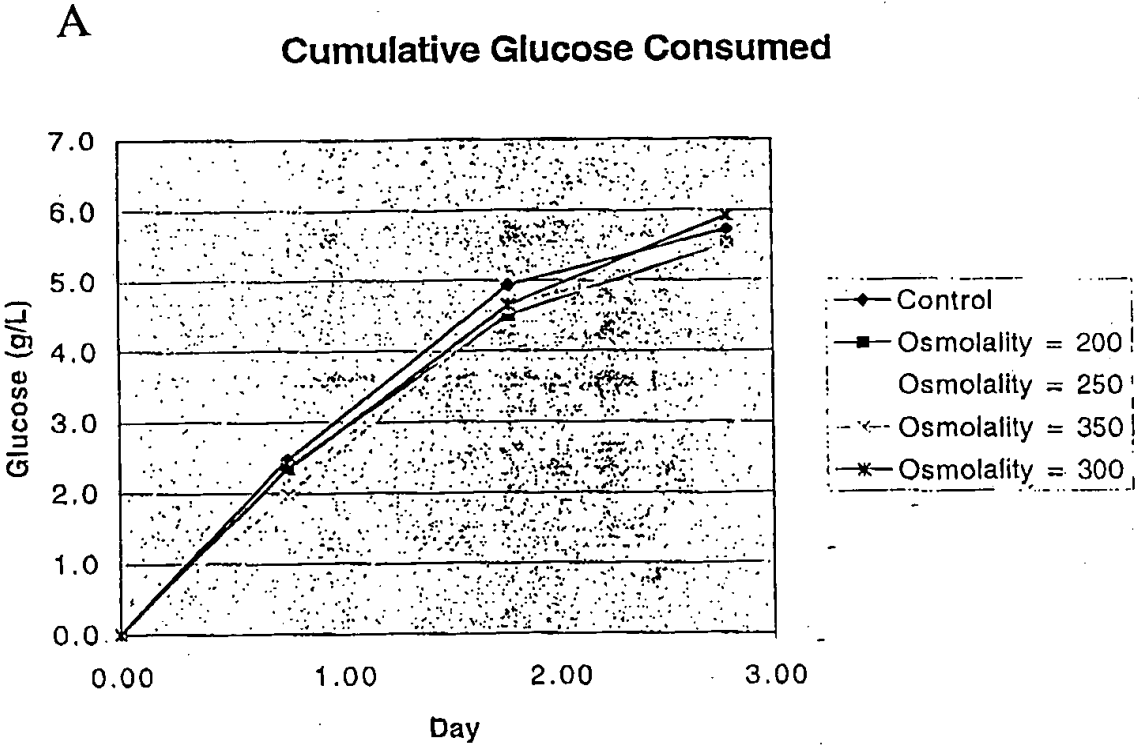

Total Cell Density
TCD (10^5 c/mL)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
Day
Control
Osmolality = 200
Osmolality = 250
Osmolality = 300
Osmolality = 350

Figure 33

A


Cumulative Glucose Consumed
Glucose (g/L)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.00
1.00
2.00
3.00
Day
Control
Osmolality = 200
Osmolality = 250
Osmolality = 350
Osmolality = 300

B

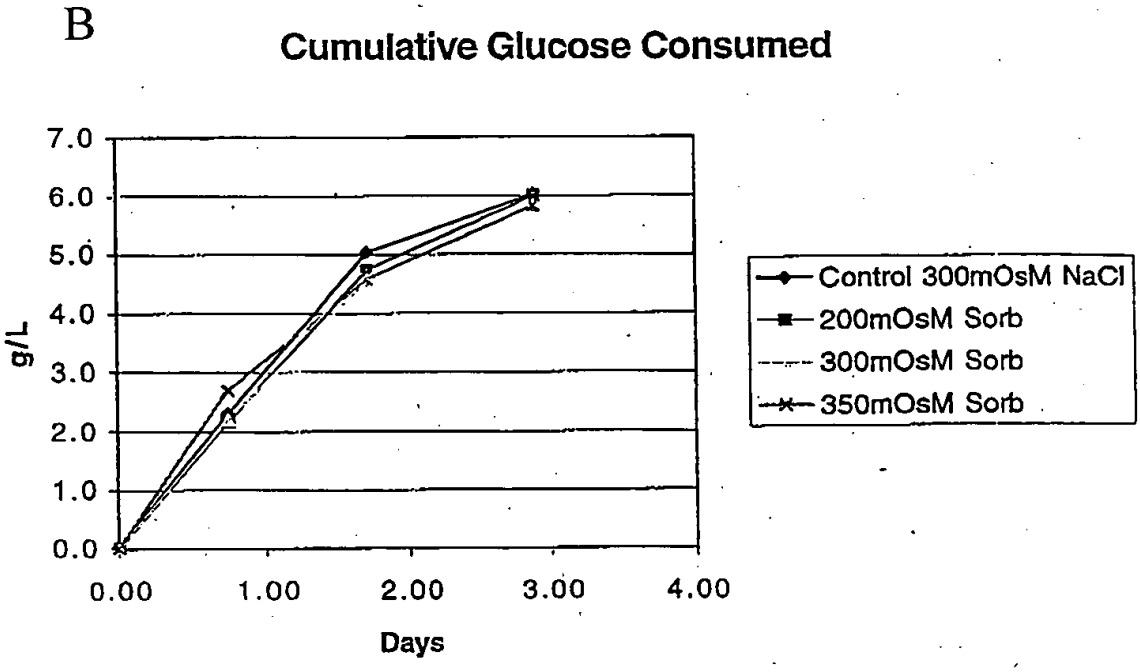
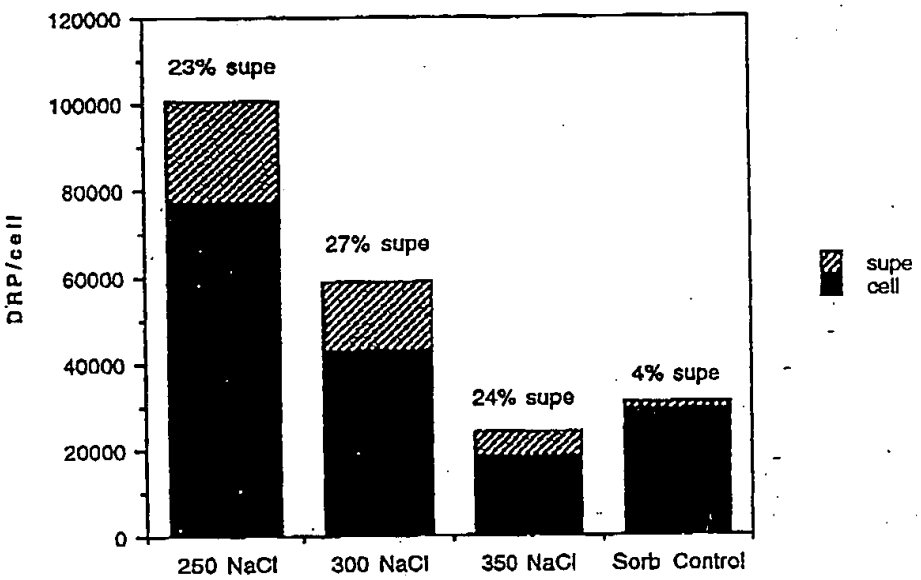
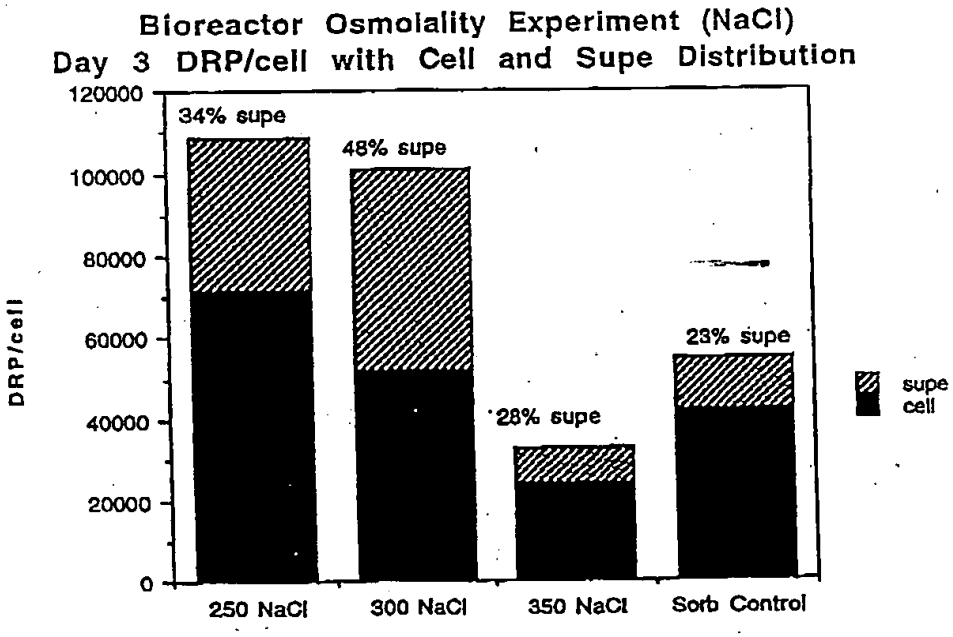

Cumulative Glucose Consumed
g/L
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.00
1.00
2.00
3.00
4.00
Days
Control 300mOsM NaCl
200mOsM Sorb
300mOsM Sorb
350mOsM Sorb

Figure 34

A

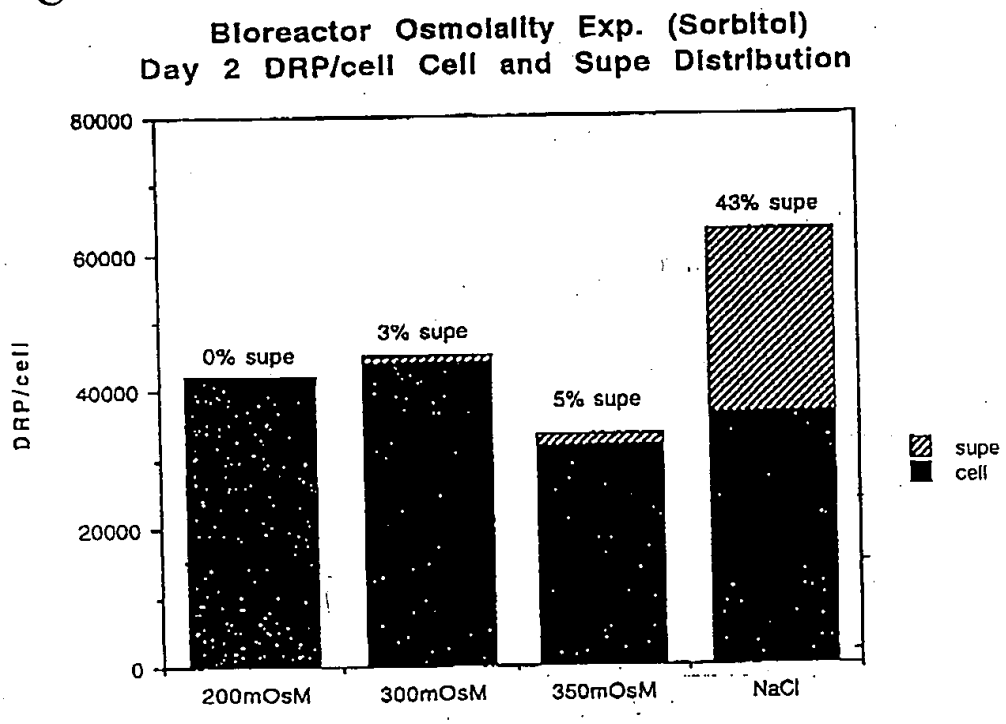


B

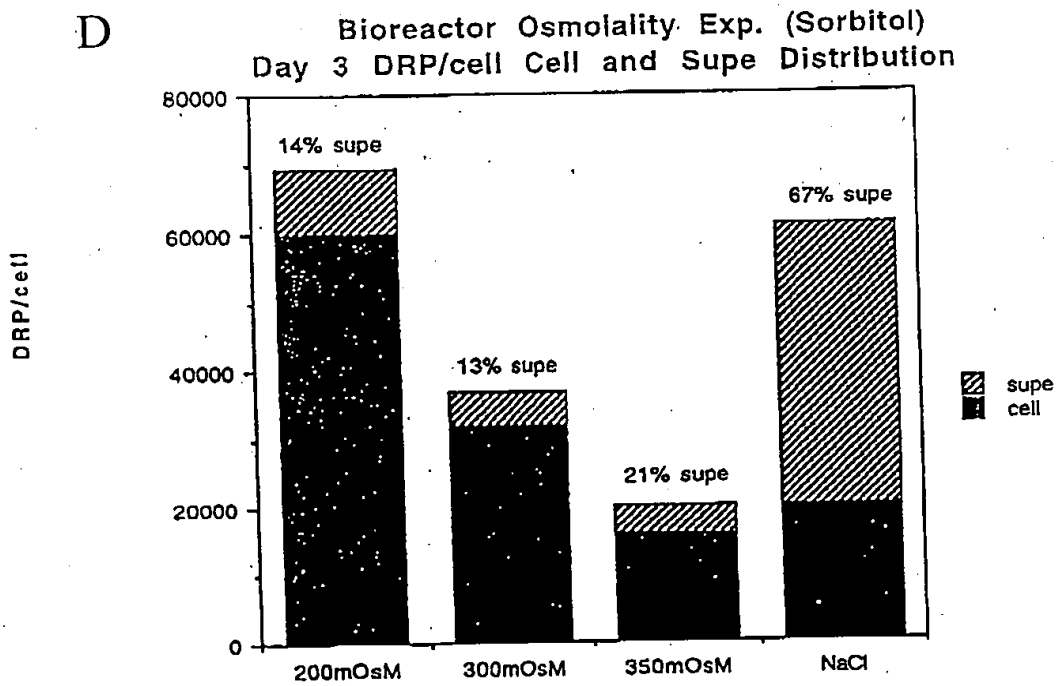


Figures 35A and 35B

C

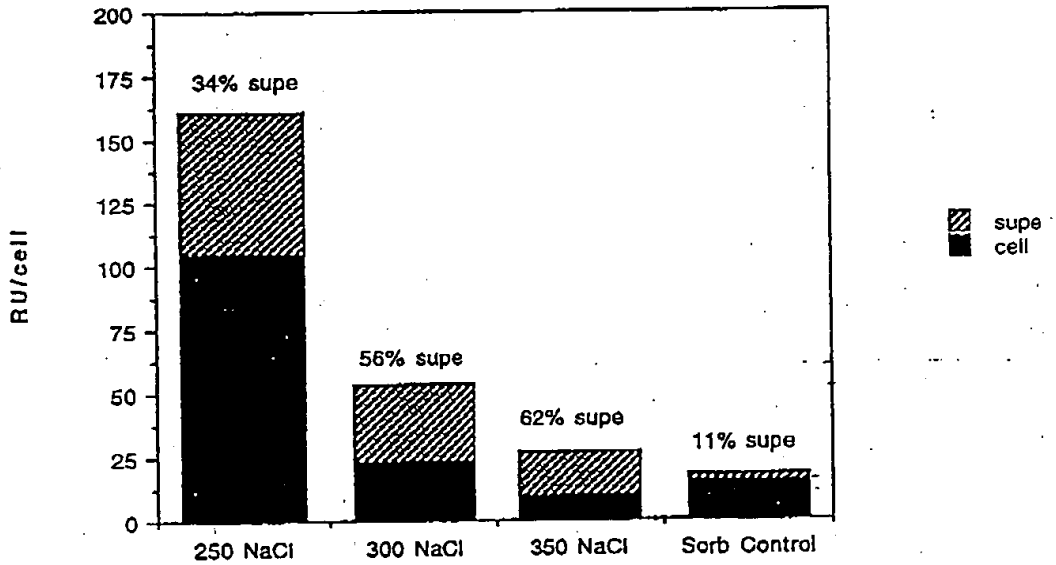


D

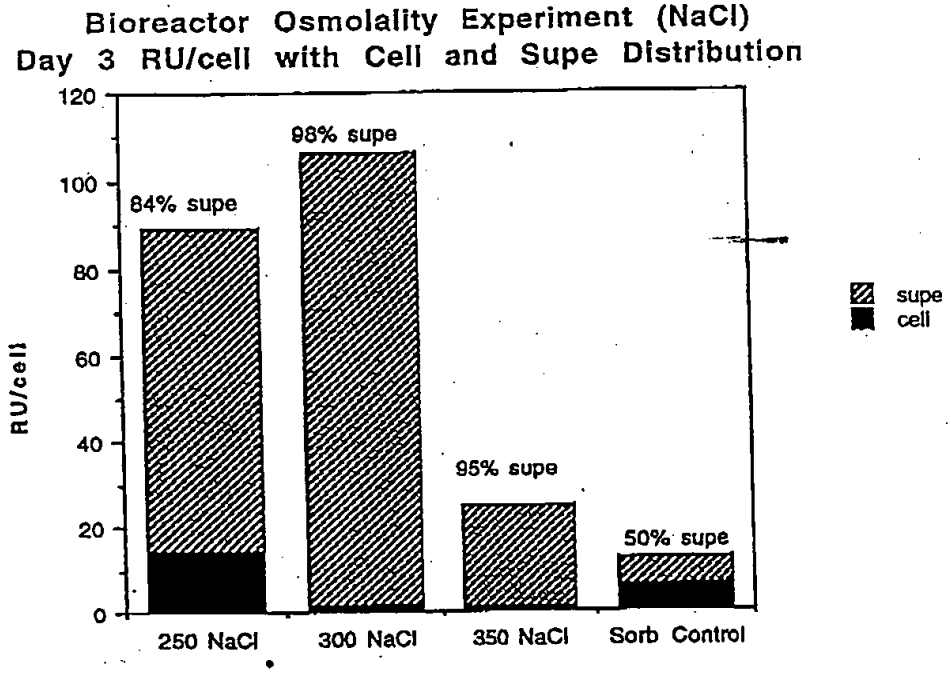


Figures 35C and 35D

A

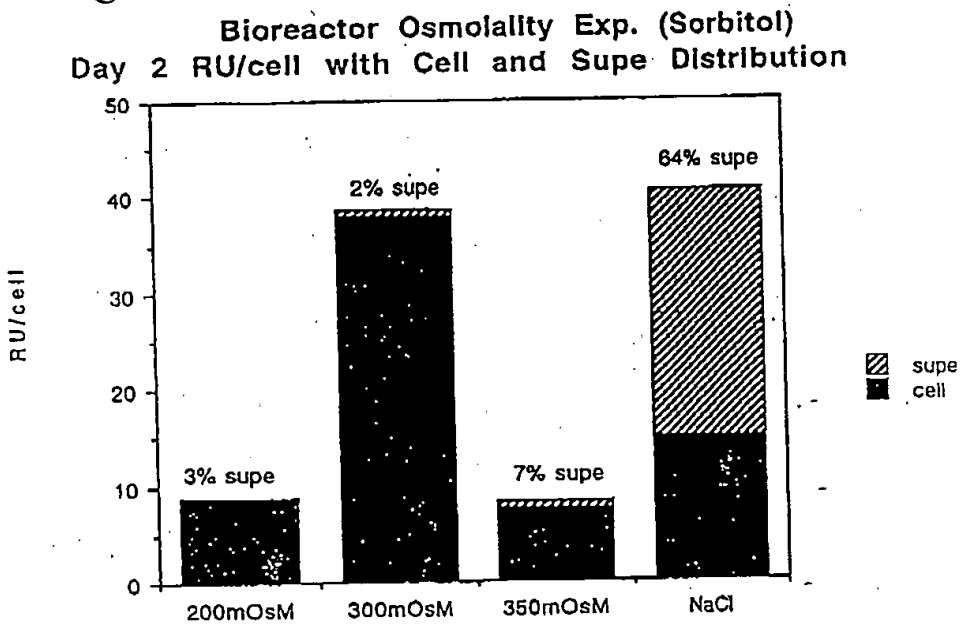


B

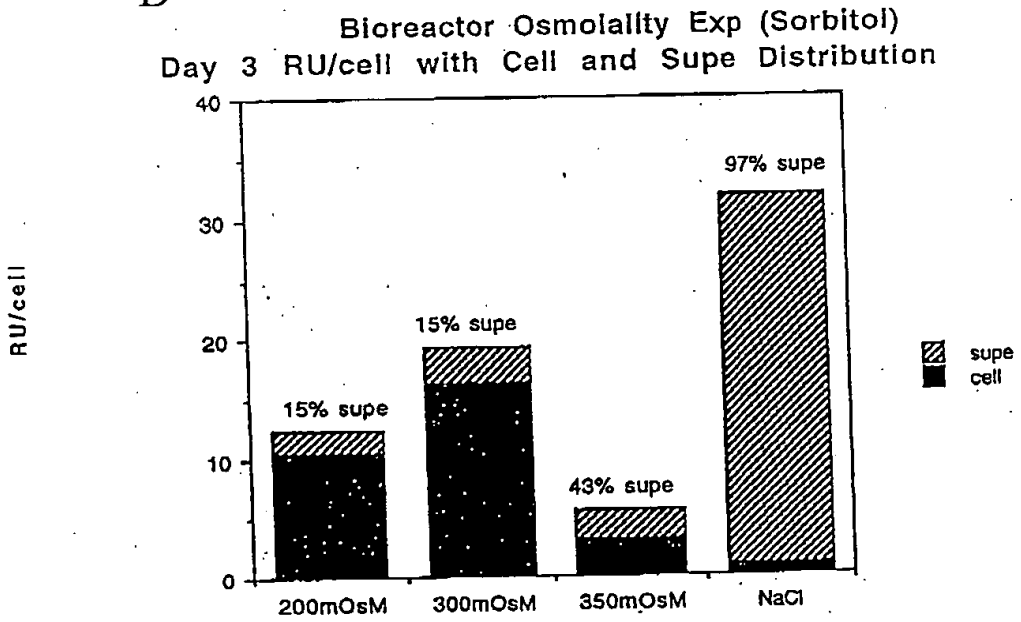


Figures 36A and 36B

C

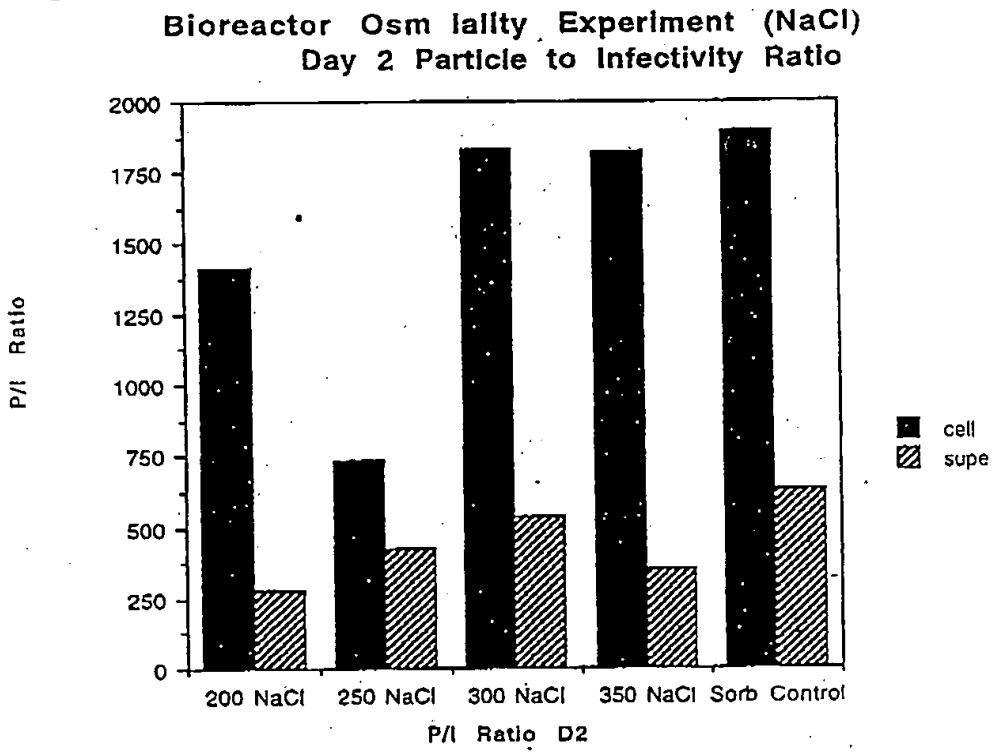


D

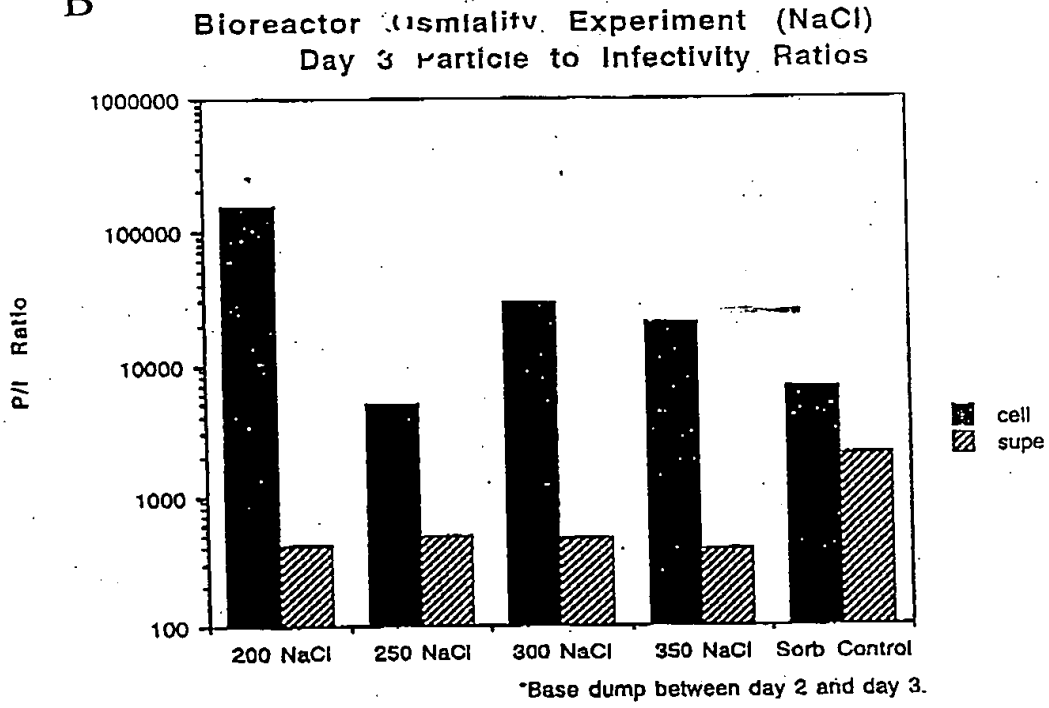


Figures 36C and 36D

A

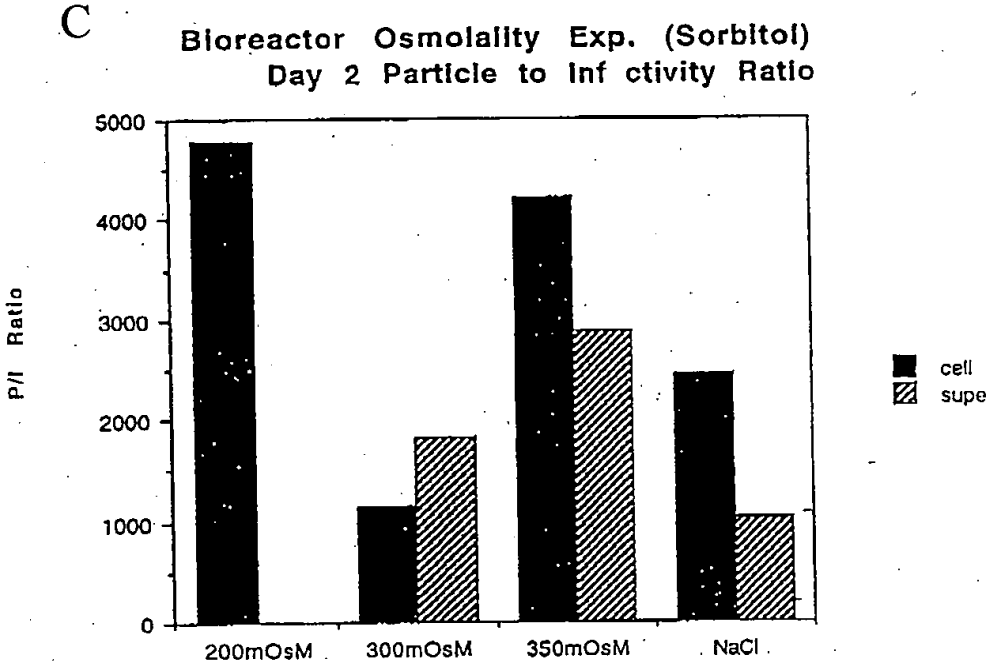


B

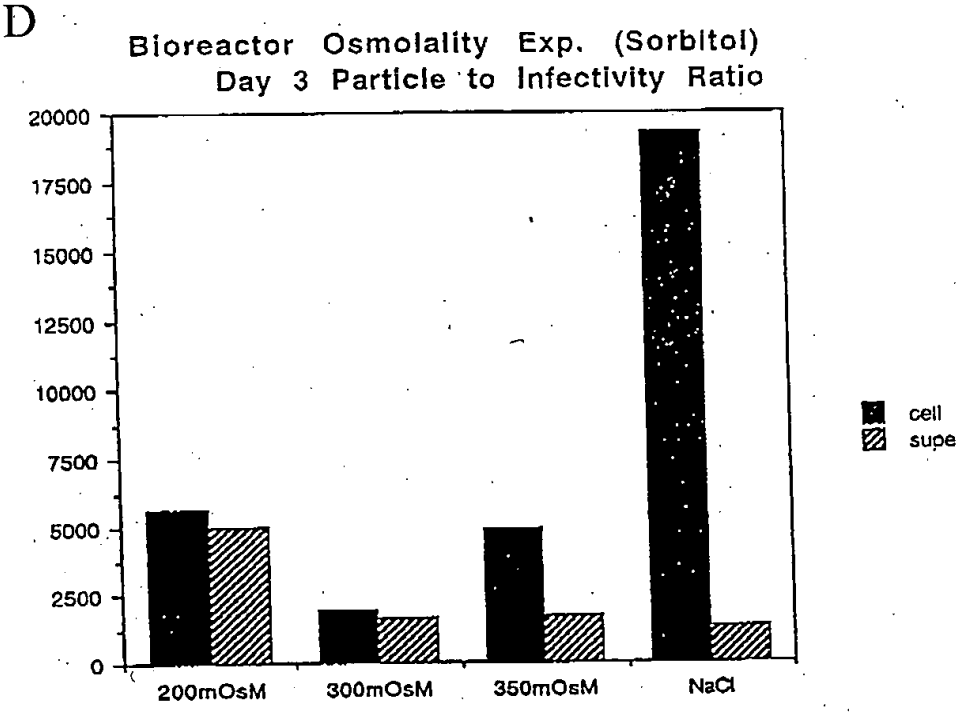


Figures 37A and 37B

C



D



Figures 37C and 37D